17638

NATIONAL LIBRARY
OTTAWA

CANADA

BIBLIOTHÈQUE NATIONALE
OTTAWA

NAME OF AUTHOR.. Tadashi Nishizawa

TITLE OF THESIS.. Morphological and functional changes in the calf lung after total artificial heart replacement

UNIVERSITY.....

DEGREE FOR WHICH THESIS WAS PRESENTED.. Master of Science

YEAR THIS DEGREE GRANTED..... Fall, 1973

Permission is hereby granted to THE NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(Signed) Tadashi Nishizawa

PERMANENT ADDRESS:

1-16-8, Shinkoiwa
Katsushika-Ku
Tokyo, Japan

DATED.. June 21 1973

NL-91 (10-68)

THE UNIVERSITY OF ALBERTA

MORPHOLOGICAL AND FUNCTIONAL CHANGES IN THE CALF LUNG AFTER TOTAL ARTIFICIAL HEART REPLACEMENT

by

© TADASHI NISHIZAWA,

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

IN

EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

FALL, 1973

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled Morphological and Functional Changes in the Calf Lung after Total Artificial Heart Replacement submitted by Tadashi Nishizawa in partial fulfilment of the requirements for the degree of Master of Science in Experimental Surgery.

.....
Supervisor

.....

.....

.....

Date June 20, 1973

ABSTRACT

Both a sac-type and a diaphragm-type air driven artificial heart capable of supporting the circulation of human-sized animals have been designed and made. Similar heart units have been orthotopically planted into the chest of calves to evaluate their performance and to further define pulmonary complications.

Acute pulmonary complication subsequent to initiation of pumping has remained one of the serious problems since the development of the artificial heart commenced. When cardiopulmonary bypass was used to support the animals during the operation, they suffered from acute pulmonary complication, with varying degrees of severity, after pumping with an artificial heart.

The natural heart in 22 calves was replaced with a total artificial heart.

Most of the animals showed a mean pulmonary arterial pressure between 40 and 65 mm Hg at a maximum, with a mean pH of 7.40, oxygen saturation of 73%, and carbon dioxide pressure of 35 mm Hg after five minutes of pumping. The pulmonary arterial pressure then decreased gradually to less than 30 mm Hg between 30 minutes and one hour after pumping. The arterial oxygen saturation increased to 88% with an increase in pH and a decrease in carbon dioxide pressure after one and a half hours of pumping.

Of the three animals that showed pulmonary arterial pressure higher than 70 mm Hg after pumping, two died due to severe acute pulmonary congestion with the arterial oxygen saturation less than 40%.

The two animals that underwent cardiopulmonary bypass for approximately two hours also died due to severe acute pulmonary edema.

Low cardiac output due to compression of the inferior vena cava by the heart and convulsions caused by thromboembolism were two of the most common causes of death in the animals that were allowed to breathe spontaneously after the chest was closed. After the animals suffered from low cardiac output, the pulmonary function gradually deteriorated and the result was severe metabolic acidosis in the animals. Approximately an hour before termination of the experiment, the pulmonary arterial pressure increased once again, as the arterial pH decreased with base excess -12 milliequivalents per liter. After the animals suffered from minor convulsions, they developed either respiratory acidosis or metabolic acidosis. As the arterial pH decreased with a decrease in base excess, the pulmonary arterial pressure increased gradually and finally reached 44 mm Hg.

ACKNOWLEDGMENTS

The help given by many towards the completion of this project is remembered with gratitude.

To the following my thanks are especially due:

Dr. C.M. Couves for his patience and continual support in the supervision of this project.

Dr. K. Kowalewski for his continual encouragement.

Dr. T.K. Shnitka for his kind assistance and numerous suggestions in interpreting pathohistology.

Mr. D.T. Morris for his construction of the artificial hearts and continual cooperation in this project.

Dr. W.A. Griswold for his cheerful surgical assistance beyond the call of duty.

Dr. R. Jones for his kind assistance in measuring and calculating cardiac output.

Mr. A. Wells and Mr. J. Soldan for their constant, cheerful, and untiring technical assistance.

Mr. R. Orchard and Mr. G. Wharton for their cheerful acceptance of long hours, making the experimental work possible.

Mr. T. Pachkowski, Mrs. M. McCubbin, Mrs. A. Klein, and Mrs. V. Maruszeczka for their biochemical determinations.

Mr. K. Lazenby and Mrs. M. Newman for their histological preparations.

Mr. I. Yamamoto for his technical assistance in the construction of the artificial heart.

Mrs. D. Gunderman for her cheerful assistance in recording and typing the experiments, and for typing this thesis.

Mrs. J. Larsen for her assistance in the typing of this thesis.

The Edmonton Civic Employees Welfare Chest Fund, the Alberta Heart Foundation and the Medical Research Council of Canada for providing the necessary funds to conduct this investigation.

Gainers' Ltd. and Swift Canadian Co. Ltd. for supplying bovine blood for this project.

TABLE OF CONTENTS

CHAPTER PAGE

I. INTRODUCTION

A. The Origin of the Problem 1

B. Brief Historical Review 2

C. The Present Work and Purpose of the Experiment 8

II. METHOD AND MATERIAL

A. Artificial Heart and Driving System 10

1. Artificial Heart 10

a. Sac-type artificial heart 10

b. Diaphragm-type artificial heart 14

2. Timing and Driving Device 18

B. Surgical Procedure 19

1. Preparation 19

2. Anesthesia 19

3. Establishment of Cardiopulmonary Bypass 19

4. Surgical Procedure for Total Artificial Heart Replacement 21

a. Resection of the natural heart 21

b. Insertion of the artificial heart 22

c. Priming the artificial heart 25

d. Commencement of pumping the artificial heart 26

5. Postpumping Procedure and Postoperative Management 27

C. Parameters Monitored and Tests Performed 28

D. Postmortem Examination 29

III. RESULTS AND DISCUSSION

A. Postoperative Course 31

1. General postoperative condition 31

2. Causes of death 36

Discussion 40

B. Pulmonary Complication in the Acute Phase 44

1. Postoperative pulmonary arterial pressure 45

a. Sac-type artificial heart group 50

b. Diaphragm-type artificial heart group 50

c. The treated group 53

d. Group mean PAP - time course for each group . 53

2. Postoperative systemic arterial pressure. 56

a. Sac-type artificial heart group 56

b. Diaphragm-type artificial heart group 58

c. The treated group 60

d. Group mean systemic arterial pressure - time course for each group 60

3. Postmortem pathological examination of the lungs . 63

a. Death due to acute pulmonary complication . . 65

b. Death in the acute phase 69

Discussion 72

C. Pulmonary Changes in the Subacute Phase 76

1. The Pulmonary function 79

1. Death Due to Convulsion Caused by thromboembolism. 79
2. Postmortem Pathological Examination of the Lungs. 83
Discussion 89
IV. SUMMARY AND CONCLUSIONS 94
BIBLIOGRAPHY. 99
APPENDIX. 106
1. Method of Deep Hypothermia and Rewarming 106
2. Surgical Procedure and Pumping 108
3. Results. 109
4. Discussion 114
5. Summary. 115
VITA

LIST OF TABLES

Table	Description	Page
1	Total artificial heart replacements.	32
2	Total artificial heart experiments.	33
3	Postoperative blood pressures and bypass duration.	46
4	Postoperative mean pulmonary arterial pressure following total sac-type artificial heart replacement.	51
5	Postoperative mean pulmonary arterial pressure following total diaphragm-type artificial heart replacement.	52
6	Postoperative mean pulmonary arterial pressure in the animals treated with Methylprednisolone following total artificial heart replacement.	54
7	Postoperative mean systemic arterial pressure following total sac-type artificial heart replacement.	57
8	Postoperative mean systemic arterial pressure following total diaphragm-type artificial heart replacement.	59
9	Postoperative mean systemic arterial pressure in the animals treated with Methylprednisolone following total artificial heart replacement.	61
10	Pathological findings in the lungs from animals that died due to acute pulmonary complication.	66
11	Pathological findings in the lungs from animals that died within 4 hours from start of artificial heart pumping.	70

12 Pathological findings in the lungs from animals that died after 4 hours of pumping. 84

13 Total artificial heart experiments using deep hypothermia. 111

LIST OF FIGURES

Figure		Page
1	Schematic drawing of sac-type, air driven artificial ventricle during systole.	11
2	Sac-type, air driven artificial heart with spherical ventricles and brass connectors for air driving tubes.	12
3	Aortic pressure patterns from the natural heart.	13
4	Aortic pressure patterns from a sac-type air driven artificial heart in vivo.	13
5	Schematic drawing of diaphragm-type air driven artificial ventricle during systole.	14
6	Diaphragm-type, air-driven artificial heart showing both ventricles, nylon velour silastic cuffs and dacron grafts.	15
7	Nylon velour silastic atrial cuff with four everting tapes.	16
8	Aortic pressure patterns from a diaphragm-type MK IX artificial heart in vivo.	17
9	Aortic pressure patterns from a diaphragm-type MK XII artificial heart in vivo. A MK XII heart is 25% smaller than a MK IX heart.	17
10	Schematic drawing of artificial heart timing and driving device.	18
11	Illustration of equipment for total artificial heart replacement using cardiopulmonary bypass.	21

12	The ventricles are resected at the atrio-ventricular groove and the arteries are divided close to the ventricles.	22
13	The atrial suturing cuffs are anastomosed to the natural atria in an inverted fashion then pulled upwards ready to accept the artificial ventricles.	23
14	Anastomosis between the ventricle and the atrial cuff accomplished by wiring the atrial cuff over Teflon ventricular valve supporter.	24
15	Anastomosis between the dacron graft and the natural aorta accomplished by tying the vessel over a rigid Teflon connector.	24
16	A sac-type artificial heart installed in the chest. The four small lines on the left are for monitoring pressures. The large line on the right is an air driving line.	25
17	A diaphragm-type artificial heart installed in the chest.	26
18	Illustration of the timing device and the calf in the postoperative cage.	35
19	Calf attempting to stand up in the postoperative cage.	35
20	Causes of death in animals with a total artificial heart.	37
21	Causes of death in animals with a sac-type artificial heart.	38
22	Causes of death in animals with a diaphragm-type artificial heart.	39

23	Cause of death and artificial heart pumping time.	39
24	The postoperative maximum pulmonary arterial pressure and the duration of total cardiopulmonary bypass for each type of artificial heart used.	48
25	The duration of elevated pulmonary arterial pressure for each group.	49
26	Postoperative pulmonary arterial pressure for each group.	55
27	Postoperative systemic arterial pressure for each group.	62
28	The lung from an animal after 110 minutes of cardiopulmonary bypass and 2 hours of artificial heart pumping. Note the marked degree of edematous congestion.	64
29	The lung from an animal that had a maximum pulmonary arterial pressure of 75 mm Hg (sacrificed after 30 minutes of artificial heart pumping). Note the marked intraalveolar hemorrhage.	67
30	The lung from an animal that had a maximum pulmonary arterial pressure of 70 mm Hg (sacrificed after 8 hours of artificial heart pumping). Note the marked degree of interlobular edema, intraalveolar hemorrhage and edema.	67
31	The lung from an animal after 110 minutes of cardiopulmonary bypass and 2 hours of artificial heart pumping. Note the intraalveolar edema.	68

32	The lung which was mechanically compressed by the artificial heart. Note the subpleural and intra-alveolar hemorrhage.	71
33	The lung from an animal that suffered from low cardiac output (sacrificed after 4 hours of MK IX artificial heart pumping). Note the marked intraalveolar edema and perivascular hemorrhage.	72
34	The change in mean pulmonary arterial pressure and pH at termination of the experiment in animals that died due to low cardiac output.	78
35	The change in mean pulmonary arterial pressure and pH at termination of the experiment in animals that died due to convulsions.	81
36	Blood pressures from an animal that had the first minor convulsion after 24 hours of pumping.	82
37	The lung from an animal with a MK IX artificial heart after 8 hours of pumping. Note the perivascular hemorrhage and intraalveolar edema.	85
38	The lungs from an animal with a sac-type artificial heart after 31 hours of pumping. Note the marked congestion, atelectasis, hemorrhage and edema.	86
39	The lung from an animal after 33 hours of artificial heart pumping. Note the congestion, intraalveolar edema and fibrin platelet thrombi in vessels.	87

40	The lungs from an animal that died soon after the first major convulsion (sacrificed after 33 hours of artificial heart pumping). Note the moderate congestion in the lower lobes.	88
41	The section of the pulmonary artery from an animal that had the first major convulsion after 33 hours of a MK XII artificial heart pumping. Note a fibrous fibrin embolus at the junction between a large pulmonary artery and a small pulmonary artery. The same material was found in the vicinity of valves and at the junction between the diaphragm and the housing of the artificial heart.	88
42	A calf is cooled in an ice water tub. After the body temperature falls below 28°C, the animal is ventilated manually and hyperventilated to cause as much respiratory alkalosis as possible prior to circulation arrest.	107
43	Body temperature course during heart replacement with deep hypothermia.	108
44	Postoperative acid-base balance of animals replaced with a sac-type artificial heart using hypothermia.	112
45	The change in mean pulmonary arterial pressure and pH at termination of the experiment (using deep hypothermia).	113
46	The change in postoperative platelets count from animals using cardiopulmonary bypass and deep hypothermia.	113

CHAPTER I

INTRODUCTION

A. The Origin of the Problem

Why is there a need for the development of artificial hearts? This question is partially answered by considering the Public Health data and statistics on heart disease. According to the latest "Causes of Death, Canada", ischemic heart disease alone accounts for about 50,000 of the 160,000 deaths in Canada within the period of one year. These statistics show heart disease as the leading cause of death, responsible for about 50 percent of all deaths. Malignant neoplasm, the next most common cause, is responsible for less than 15 percent of all deaths. Approximately 200,000 people are seriously handicapped by heart disease in Canada. A National Health Survey in the United States indicates that one in four American adults has definite or suspected heart disease.

Basically, there are only three current therapeutic techniques for the treatment of patients with heart disease. These are chemotherapy, surgery and mechanical intervention. The role and value of each of these stands unquestioned. Each approach has its unique advantages and limitations in relation to the specific disability being treated. However, when the myocardium is irreversibly damaged, a replacement heart is the only treatment. It is possible that the time will come when homotransplantation of the human heart becomes a reality. Even when the immunological problem which is at present the greatest barrier, is solved, the ethical and physical problems in the

procurement of healthy human hearts will remain. Heterologous transplantation might be an answer, but the immunological problem is more severe than for homotransplantation. The rapid and remarkable development of medical engineering and plastic technology in recent years has opened another approach to the total replacement of the heart, the use of an artificial heart.

An artificial heart might be used either temporarily, until an appropriate homologous heart becomes available, or as a permanent replacement. This will only be possible in the future when perfect component materials and energy sources are available.

B. Brief Historical Review

In 1937 Demikhov of Russia first attempted to implant a mechanical heart inside the body.[41]* He performed three such experiments implanting in animals a pumping contrivance that was driven by a rotating shaft powered from outside and inserted into the animal through a tube in the chest wall. Demikhov returned to this investigation with five more experiments in 1958, but as far as we can learn, he has not pursued the work further.

Salisbury[70] in his address to the 1957 Annual Meeting of the American Society for Artificial Internal Organs, was probably the first person in the United States who dared to speak openly about the possibility of implanting an artificial heart inside the chest. On December 13, 1957 Kolff and his coworkers[2] at the Cleveland Clinic

---

*Numbers in brackets denote references on page

Foundation placed an air-driven artificial heart made of polyvinyl chloride into the chest of a dog after removing its own heart. The chest was closed and circulation was maintained for 90 minutes. The heart was driven by a reciprocating pump and an oscillating column of air via a plastic tube through the chest wall. This was the beginning of many experiments which were conducted under Kolff's direction. In 1959 the Department of Artificial Organs, Cleveland Clinic Foundation, began to study the artificial heart in earnest. At the beginning of their study electrically driven artificial hearts were used. These were an electro-magnetic five solenoid-type[42] and a pendulum type.[33] However, these electrically driven artificial hearts were mechanically unsound, heavy and not efficient.

Among the early investigators of this problem elsewhere were Selwyn McCabe at the National Institute of Health, U.S.A.,[54] Bert Kusserow at Vermont College of Medicine,[43] William Fry and Francis Fry at the University of Illinois,[41] Domingo Liotta in Argentina[52] and Kajuhiko Atsumi in Japan.[7,36] These investigators used dogs as the experimental animal. Liotta developed pumps employing membranes, bellows and rollers, and reported a survival time in dogs of 13 hours in 1959.[52] These were very good results for that time.

In 1960 investigators began using compressed air as an external power source for artificial hearts.[74] Since all dogs which survived for 20 hours after total replacement of the natural heart with an artificial heart died from multiple thomboemboli, Akutsu et al changed two conditions. The material for the artificial heart was changed from polyurethane to silastic and the experimental animal from

dog to calf.[3]

Thus, by 1963, the difficulties with thrombosis in dogs led to the use of calves as the experimental animal for further work. An additional advantage was that the animal used had a heart comparable in size to that of the human adult. The calves apparently had normal circulation for periods of over 24 hours without the occurrence of severe thrombosis, whereas dogs died within that time from thrombosis. However, in calves another and unexpected complication occurred. A strange type of pulmonary insufficiency prevented the calves from surviving longer than five hours.[5] Immediately after the artificial heart started pumping and the cardiopulmonary bypass was stopped, the calf became anoxic and acidotic due to insufficient oxygenation by their own lungs. Also, a high pulmonary artery pressure was noticed although there was no atelectasis and no pulmonary edema. Similar impairment in pulmonary function was well known after prolonged cardiopulmonary bypass in dogs and in men, but it was rare. The difference in species and in age of the animal could be factors. However, the exact reasons have not been completely resolved even at the present time.[38]

In the years following many short-lived designs were developed. For example, in 1966 Woodward from the U.S. Army's Harry Diamond Laboratories developed an artificial heart based on the fluid-amplification technique. The fluid amplifier was a mechanical analogue of the electronic tube: a stream of air or another fluid entering a system of channels was amplified or switched from one outlet to another controlled by jets from the side. Woodward sustained a calf with this

heart for 24 hours.[85] Burns et al, of the Indiana University School of Medicine, also developed a motor and fluid driven pump which resulted in survival times of up to 18 hours.[17] Since these types of artificial heart were excessive in weight and size, the inferior vena cava was often compressed by the lower corner of the housing. A high pressure gradient between the inferior vena cava and the right atrium resulted. Simultaneously, devices with active filling of the ventricles were tried. For example, vacuum was applied during diastole, especially when high mitral valve resistance existed, to achieve proper filling of the ventricle. Another idea was contraction of the atria, which is theoretically feasible. However, to date the only artificial heart which has a functioning artificial atrium is McCabe's artificial heart made in 1957.[54]

To avoid compression of the inferior vena cava by the heart, light weight, round shaped artificial hearts of the sac-type or diaphragm-type took precedence by 1968.[64] To obtain good venous return into the right atrium, soft material was used for the atria instead of Dacron impregnated with silicone.[63,66]

A group in the Division of Artificial Organs at the University of Utah, led by W. Kolff, and a second group from the Department of Surgery, University of Mississippi Medical Center led by T. Akutsu, used sheep as the experimental animal instead of the calf in order to avoid pulmonary insufficiency immediately after termination of cardio-pulmonary bypass.[45,4] In 1969, using a sac-type, air-driven heart which could be implanted inside the pericardial sac, Akutsu and his coworkers sustained circulation for up to 55 hours. Pulmonary

insufficiency was less severe than in calves, however, several problems arose using sheep as the experimental animal. Tears in the anastomoses of great vessels, a severe bleeding tendency after extracorporeal circulation, a small chest cavity and the necessity to use adult sheep were troublesome.[79] These investigators then returned to the use of calves.

On April 4, 1969 Cooley of Houston, Texas, first implanted an artificial heart in a human. A 47 year old male who was diagnosed as having advanced coronary artery occlusive disease associated with complete heart block and extensive left ventricular fibrosis with aneurysm formation [classified as functional class III, bordering on IV (New York Heart Association)] received this heart. The pneumatically controlled, double-ventricle cardiac prosthesis was a diaphragm-type of pump. It was fabricated of Dacron embedded in silastic. The same concept had been tested in previous work by Liotta with non-fabric-lined pumps implanted into dogs as an orthotopic cardiac prosthesis.[52] The patient was sustained with this artificial heart for 64 hours and then received a cardiac allograft. Death from respiratory failure occurred 32 hours following the second operation.[20]

Before 1969 many sac-type prosthetic hearts had been made for experimental implantation. The severe hemolysis produced by the sac-type prosthesis was caused by the opposite walls of the sac rubbing against each other. Mechanical crushing or damage by high shear stress disrupted red blood cells.

In 1970 Kwan-Gett at the University of Utah designed a hemispherical diaphragm-type ventricle.[47] When the bases of a left and

right ventricle were attached to each other the complete heart was nearly spherical in form. The rate of hemolysis of a hemispherical left ventricle, used as a left heart bypass, was much less than that of a silastic sac-type ventricle. The silastic diaphragm-type ventricle produced a plasma hemoglobin level of 0.25 milligrams percent per hour for the last 16 hours of pumping, while the silastic sac-type ventricle produced a plasma hemoglobin level of 6.7 milligrams percent per hour. Since the modified diaphragm ventricle could be implanted within the pericardial sac of the experimental animal, compression of the inferior vena cava was minimized.

In 1971 Akutsu et al and Kolff et al achieved over 100 hours survival with a total artificial heart, using calves as experimental animals instead of sheep.[79, 44] However, with the longer survival, blood trauma became more serious and more difficult to try to reduce. The valves of the prosthetic heart had been altered and several different blood contact surfaces had been used. In order to eliminate the initial blood trauma due to cardiopulmonary oxygenation, deep hypothermia and complete circulatory arrest were employed.[44] With this method blood evaluation at the commencement of pumping showed levels of fibrinogen and platelets higher than those found following cardiopulmonary bypass. At autopsy the lungs were in better condition than the lungs from experiments using cardiopulmonary bypass. However, a fall in platelets and fibrinogen and an increase in whole blood clotting time were soon observed. Evidence of disseminated intravascular coagulation occurred in the calves which survived for more than 24 hours.

At present a nuclear-powered artificial heart has been

implanted in an experimental animal. There are problems with this device related to size and increase of body temperature.[60, 83] Kolff and his coworkers at the University of Utah, using a hemispherical diaphragm-type artificial heart, which had a surface of Dacron fibrils coated with fetal fibroblasts, have had a calf survive longer than 10 days.[31]

Many researchers in areas other than the United States, such as the U.S.S.R.,[45] Europe[1, 39] and Japan[40] are investigating artificial heart possibilities.

C. The Present Work and Purpose of the Experiment

At present both a sac-type and a diaphragm-type artificial heart have been designed and produced. Different materials have been used for these artificial hearts in an attempt to decrease thromboembolism formation. However, many factors contribute to the failure of these artificial hearts: e.g. acute pulmonary complication, inadequate venous return due to compression of the inferior vena cava by the artificial heart, thromboembolic phenomena, disseminated intravascular coagulation, as well as progressive diastolic hypotension with resulting widening of the pulse pressure. The sum of these phenomena has been called the "artificial heart syndrome".[24]

Pulmonary complications have remained one of the serious problems in the development of an artificial heart. Although some experimental animals with an artificial heart did not suffer from acute pulmonary complication and survived for a long time, most experimental animals did suffer from this complication in varying degrees of severity.

As a result artificial hearts have been orthotopically planted into the chest of calves in an attempt to further define these pulmonary complications.

CHAPTER II

METHODS AND MATERIALS

A. Artificial Heart and Driving System

1. Artificial heart

Two different types of artificial heart have been designed and used for total heart replacement in calves. The earlier model was a biventricular, air-driven, sac-type artificial heart.[57,58,61] The later model was a biventricular, air-driven, diaphragm-type artificial heart.[62]

a. Sac-type artificial heart

This heart design is that of a ventricle sac-type driven by compressed air delivered by a simple control mechanism (Fig. 1). The heart is four-chambered and contains four one-way check valves. The shape is more globular than that of the natural heart (Fig. 2). It consists of two independent sides to facilitate atrial anastomosis. Each atria consists of a length of dacron graft fitted with a dacron velour suturing cuff. The aortic and pulmonary arteries connect to the natural arteries by means of Teflon cannulae.

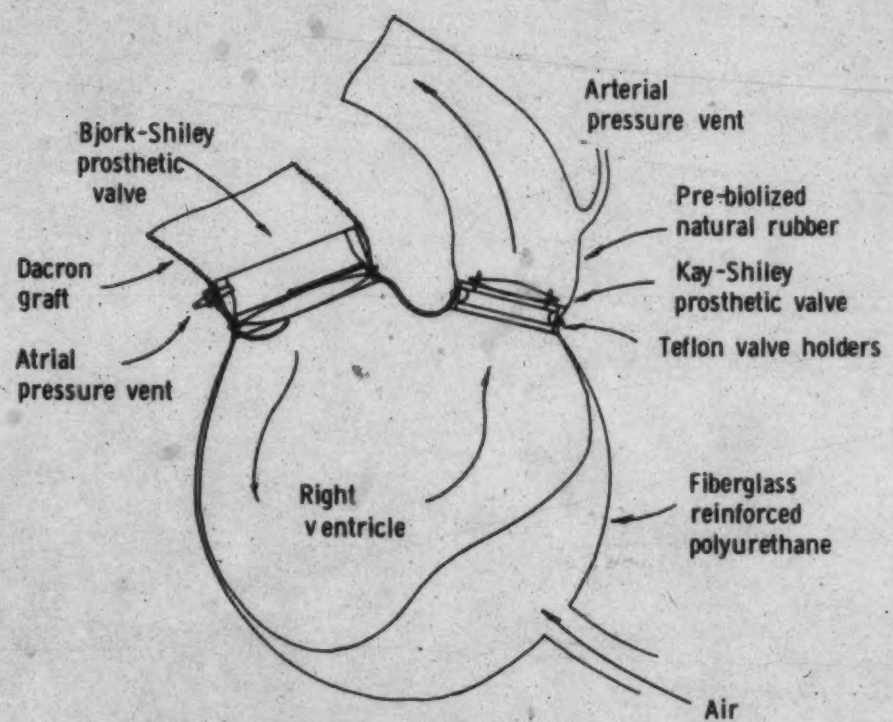

Fig. 1 Schematic drawing of sac-type, air-driven artificial ventricle during systole.

Fig. 2 Sac-type, air-driven artificial heart with spherical ventricles and brass connector for air driving tubes.

The sacs and arteries are made of natural rubber by dipping male wax molds into liquid latex. The natural rubber used is prebiolized by bonding heparin to the surface to enhance its antithrombogenic properties. Commercially available heart valves are incorporated and the ventricles are encased in a brushed-on coating of clear polyurethane. The ventricles are fitted with vents into all chambers for pressure monitoring, and tubes are inserted into the spaces between the sacs and casings to provide ports for the driving air.

The heart weighs 500 grams, occupies 700 milliliters of space and has ventricular volumes of 150 milliliters. The heart with its output dependent upon venous filling pressure obeys Starling's Law. It most closely duplicates the action of the natural heart, providing

a pulsatile flow of near natural rate, volume and velocities, and may possess a shape similar to that of the natural heart (Fig. 3, 4).

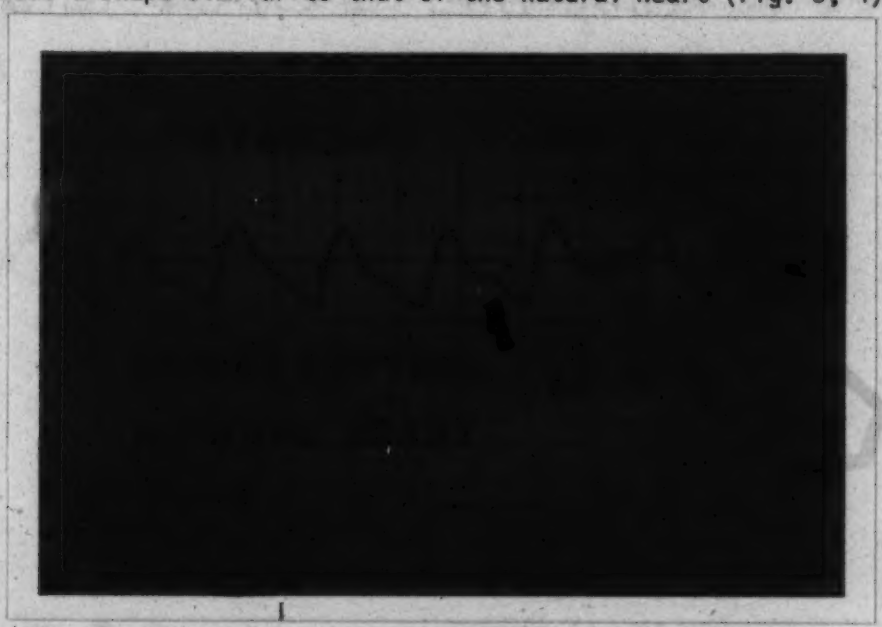

Fig. 3 Aortic pressure patterns from the natural heart.

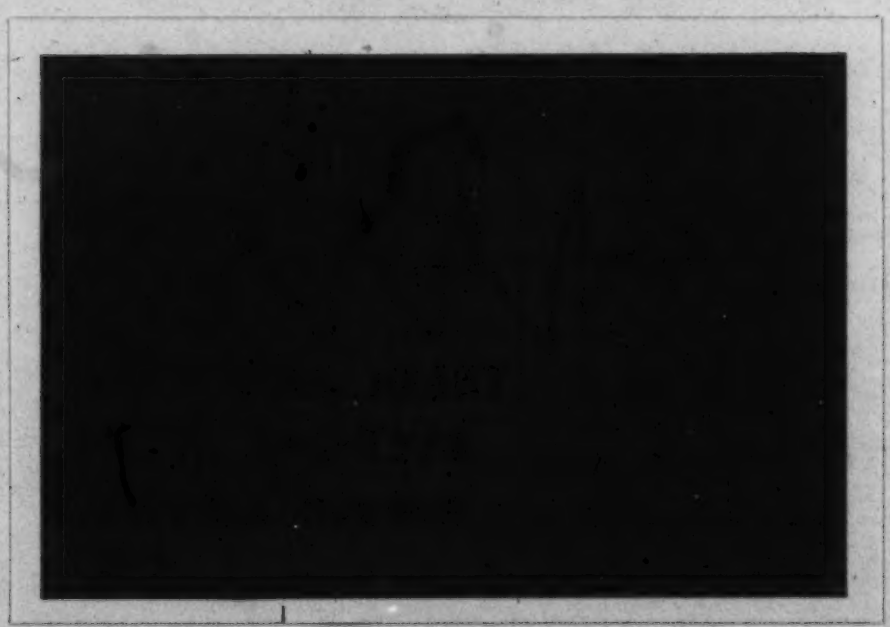

Fig. 4 Aortic pressure patterns from a sac-type air-driven artificial heart in vivo.

b. Diaphragm-type artificial heart

Two kinds of diaphragm-type artificial heart have been designed, made and used. They are the earlier MK IX model and the currently used smaller MK XII model. Each consists of two independent sides (left and right ventricles)each having a silicone rubber hemispherical diaphragm that transverses over the center in two hemispherical chambers (Fig. 5).

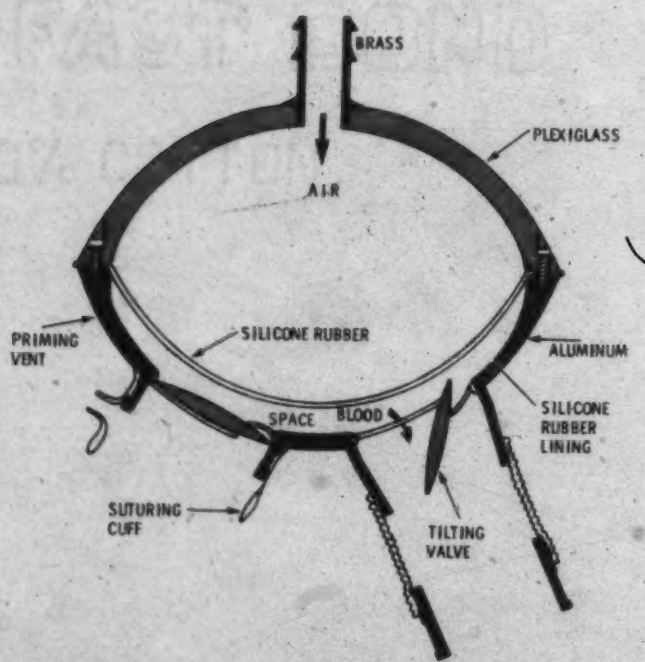

Fig. 5 Schematic drawing of diaphragm-type air-driven artificial ventricle during systole.

One chamber, the compressed air driving side of the diaphragm, is machined from clear plexiglass. The other chamber, the blood pumping side, is machined from aluminum. The aluminum side contains two one-way tilting disc-type valves and adaptors for connection to dacron grafts. These are anastomosed to the great vessels of the experimental animal. The blood pumping chambers are coated throughout with a thin film of silicone rubber (Fig. 6)

Fig. 6 Diaphragm-type, air-driven artificial heart showing both ventricles, nylon velour silastic cuffs and dacron grafts.

The atria of a MK IX artificial heart consists of a length of dacron graft fitted with an aluminum valve supporter. The atria of a MK XII artificial heart consists of a length of silicone graft and is separate from the ventricle (Fig. 7)

Fig. 7 Nylon velour silastic atrial cuff with four everting tapes.

The earlier MK IX model weighs 200 grams per ventricle and has a stroke volume of 160 milliliters. The MK XII model weighs 135 grams per ventricle and has a stroke volume of 85 milliliters. The usual cardiac outputs are 14 liters per minute for the MK IX and eight liters per minute for the MK XII. The heart rates required to achieve these outputs are 87 per minute for the MK IX and 94 per minute for the MK XII. Both models with an output dependent upon venous filling pressure obey Starling's Law. The later model, with its smaller stroke volume and higher rate, provides a more physiological output pressure wave form (Fig. 8, 9). Both models are powered by compressed air and an extra-corporeal timing device regulates the heart function.

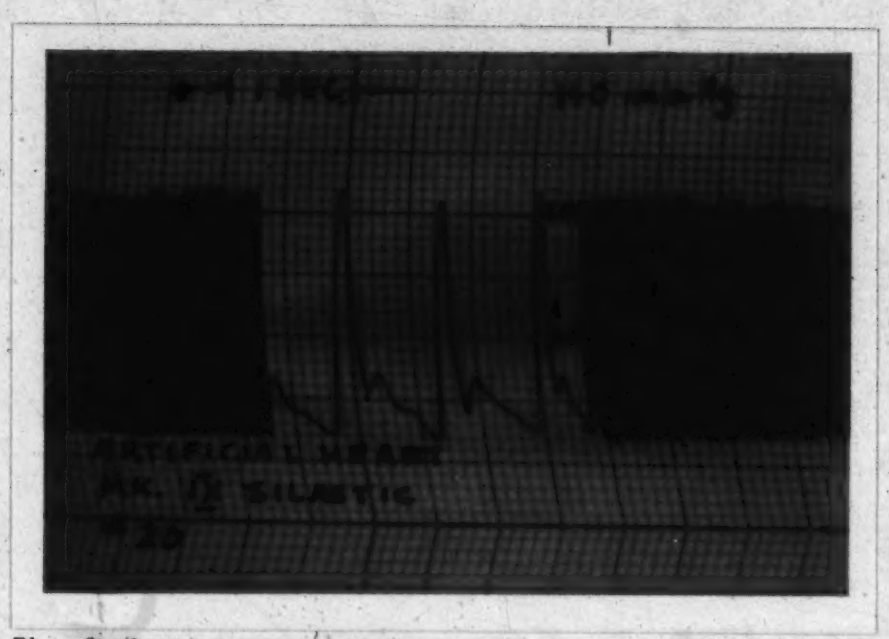

Fig. 8 Aortic pressure patterns from a diaphragm-type MK IX artificial heart in vivo.

Fig. 9 Aortic pressure patterns from a diaphragm-type MK XII artificial heart in vivo. A MK XII heart is 25% smaller than a MK IX heart.

2. Timing and Driving Device

The timing and driving system is capable of delivering compressed air of variable pressure to and from each side of the pump independently and of varying the duration of systole or diastole. Air pressure is metered by regulators and directed to and from the ventricles by threeway air-piloted solenoid valves which are manually controlled by a simple electronic circuit (Fig. 10).

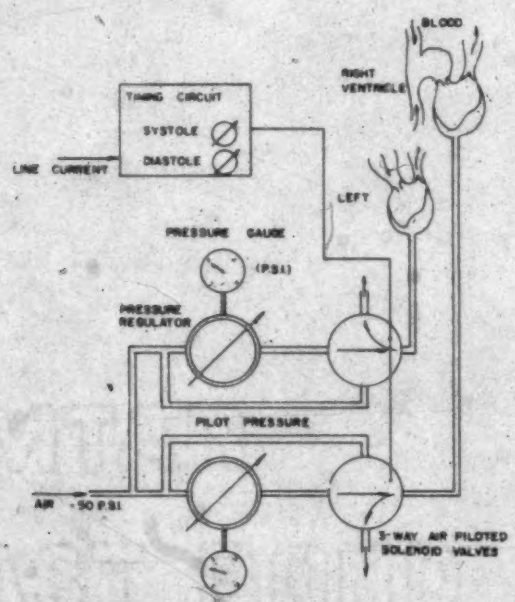

Fig. 10 Schematic drawing of artificial heart timing and driving device

Negative pressure of five to nine millimeters of mercury is imparted to both ventricles during the diastole phase.

The artificial heart is connected to the external driving system by two Vinylon tubes six feet in length and three-eighths inch in internal diameter.

B. Surgical Procedure

1. Preparation

Calves weighing between 65 and 90 kilograms were used for these experiments. They were fasted for a 24 to 48 hour preoperative period and allowed only water and milk. Penicillin, two million units administered intramuscularly, was given to the animals every other day for one week prior to each experiment. Blood for transfusion was obtained from a local slaughterhouse and stored in ACD containers (anticoagulant citrate phosphate dextrose solution) to which one million units of penicillin per liter of blood was added. Trifluopromazine, 0.2 milligrams per kilogram, and Atropine 0.02 milligrams per kilogram were given intramuscularly to the animal for premedication.

2. Anesthesia

Thirty minutes after premedication anesthesia was induced with halothane. A conical face mask and partial rebreathing system with two or three percent halothane and seven to ten liters per minute of oxygen was used. The animal was then placed on its back on the operating table and an endotracheal tube was inserted. Before the chest was opened anesthesia was maintained with 0.5 to 1.5 percent halothane and spontaneous respiration. Once the chest was opened the lungs were mechanically ventilated by an Engstrom Respirator model 200. A tidal volume of 750 milliliters with respiration rate of 18 to 20 times per minute was used to prevent alveolar collapse.

3. Establishment of Cardiopulmonary Bypass

The surgical field was shaved, washed with three percent Hexa-

chlorophane and painted with ten percent Providone-Iodine N.F. The left external jugular vein and carotid artery were exposed for a later insertion of cardiopulmonary bypass cannulae. The left subscapular artery and vein were exposed and used for arterial pressure monitoring and for an infusion line. The chest was entered through a midline sternotomy. Umbilical tapes were passed around the superior vena cava, azygous vein, hemiazygous vein, pulmonary artery and the aorta. Heparin (four milligrams per kilogram) was given intravenously prior to insertion of the venous cannulae. A #28 Bardic catheter was inserted into the left external jugular vein and positioned in the superior vena cava. A #40 Bardic catheter was inserted into the inferior vena cava via the right atrial appendage. A #20 Bardic catheter, placed retrogradely in the left common carotid artery, was used for arterial inflow.

Either a Bentley or a Travenol adult disposable oxygenator with a Sarns modular pump was used for cardiopulmonary bypass (Fig. 11). The oxygenator and circuit were primed with 1500 to 2000 milliliters of either five percent dextrose in water or Ringer's solution for a hemodilution rate of 16 to 21 percent. Blood flow to and from the heart was interrupted by occluding the vessels with the umbilical tapes passed through Tygon tourniquets. The pump flow rate was usually 50 to 60 milliliters per kilogram per minute with about 60 centimeters of gravity drainage to the heart-lung machine. Total bypass time was between 60 and 90 minutes. During the cardiopulmonary bypass the lungs were manually inflated with a pressure of 30 centimeters of water every ten minutes. Ventilation was reinstituted with 100 percent oxygen about five minutes before starting the artificial heart pumping.

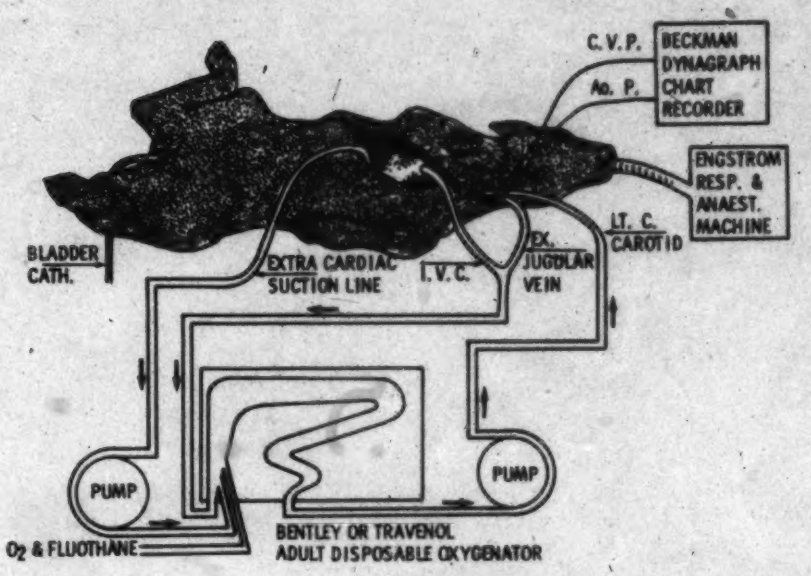

Fig. 11 Illustration of equipment for total artificial heart replacement using cardiopulmonary bypass.

4. Surgical Procedure for Total Artificial Heart Replacement

a. Resection of the natural heart

After blood flow to and from the heart was interrupted by occluding the vessels with umbilical tapes passed through Tygon tourniquets, the apex of the heart was grasped by a big Kocher's forcep. The left and right ventricles were opened at the apex, and the blood in both ventricles was aspirated. Most of the ventricular muscle was quickly excised. The pulmonary artery was resected close to the right ventricle. The remaining ventricular muscle and fatty tissue was carefully excised along the atrioventricular groove (Fig. 12). The aorta was then resected close to the left ventricle; care was taken to gently separate the aorta and the right atrium. Perforation on the right atrial wall was a major risk.

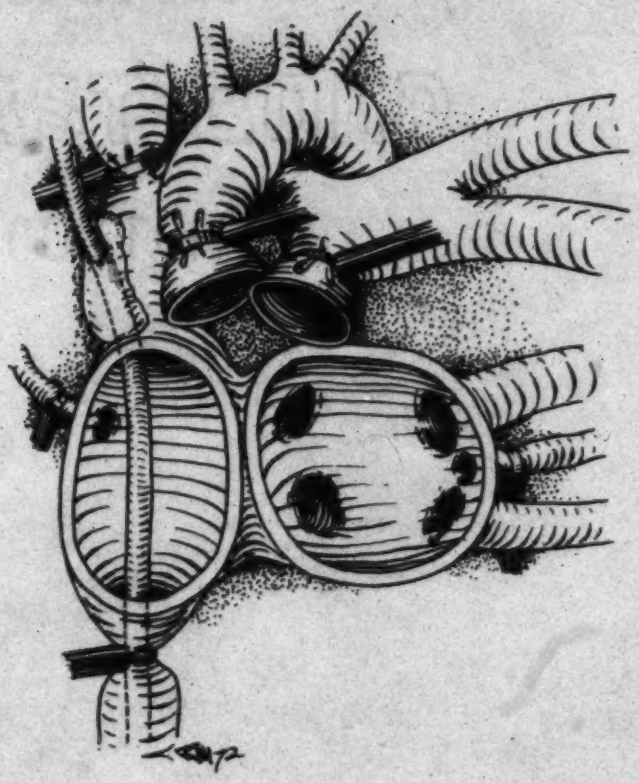

Fig. 12 The ventricles are resected at the atrio-ventricular groove and the arteries are divided close to the ventricles.

b. Insertion of the artificial heart

In the early series the rim of the atrial cuff which was attached to the ventricle was inverted into the atrium. The rims of the natural atrium and the cuff were held together with four or five Allis' forceps and then sutured in a continuous manner with 000 Mersiline. Later, the cuff which was separate from the ventricle was completely inverted into the atrium. After completing the right and then the left anastomosis, four tapes attached to the free edge of the atrial cuff

were grasped by Pean's forceps and pulled upward (Fig. 13).

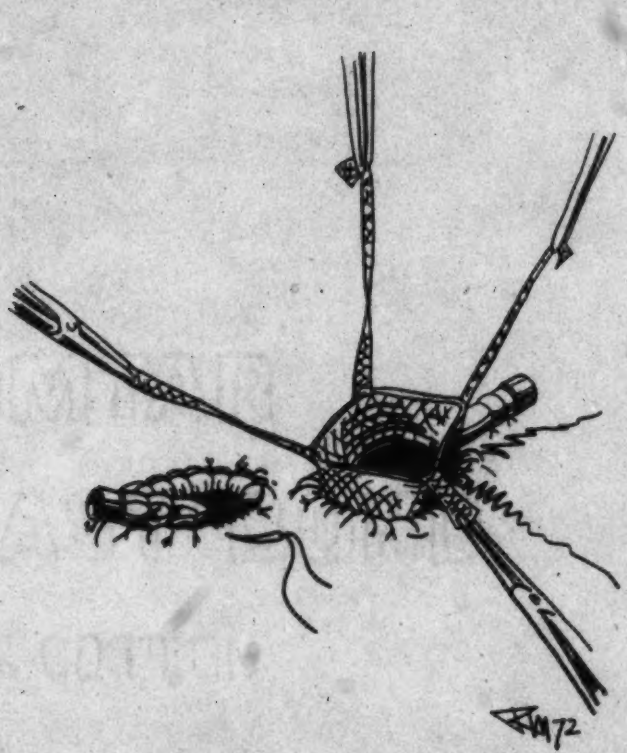

Fig. 13 The atrial suturing cuffs are anastomosed to the natural atria in an inverted fashion then pulled upwards ready to accept the artificial ventricles.

The ventricle and the atrial cuff were anastomosed by wiring the atrial cuff over the Teflon ventricular valve supporter (Fig. 14). The artificial and natural aorta were anastomosed by tying the vessel over a rigid Teflon connector (Fig. 15). The natural and artificial pulmonary artery were joined in a similar fashion. The driving lines were passed through stab incisions in the chest wall and one end of each line was attached to the driving system of the artificial heart.

Fig. 14 Anastomosis between the ventricle and the atrial cuff accomplished by wiring the atrial cuff over Teflon ventricular valve supporter.

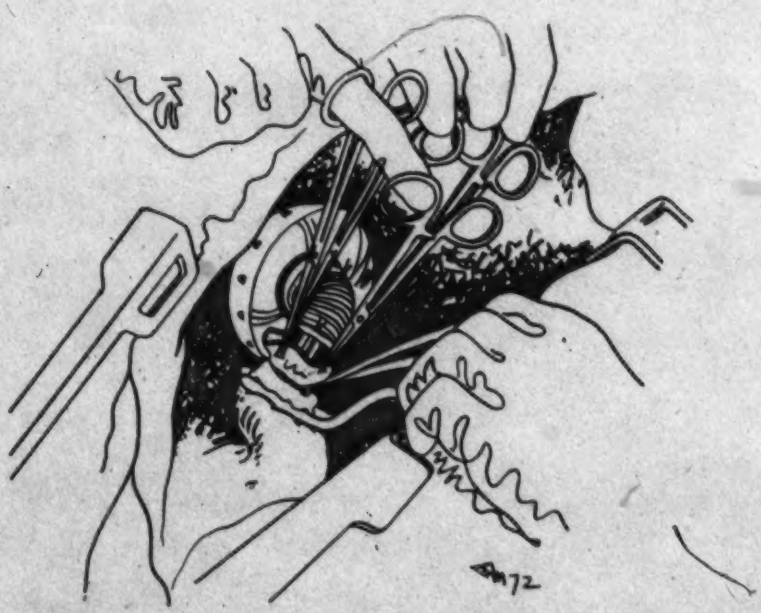

Fig. 15 Anastomosis between the dacron graft and the natural aorta accomplished by tying the vessel over a rigid Teflon connector.

c. Priming the artificial heart

Following completion of the anastomoses the tourniquet of the inferior vena cava was temporarily released and the venous drain to the pump oxygenator was partially occluded. The line to the atrial pressure transducer was used for priming the heart with ACD blood. The right artificial heart was also primed by allowing blood to flow from the inferior vena cava into the atrium; the left artificial heart was also primed with blood from the bronchial arteries. The air vent which was placed at the top of each artificial ventricle was screwed closed after the artificial heart was completely primed and all air was out of the heart (Fig. 16, 17).

Fig. 16 A sac-type artificial heart installed in the chest. The four small lines on the left are for monitoring pressures. The large line on the right is an air-driving line.

Fig. 17 A diaphragm-type artificial heart installed in the chest.

d. Commencement of pumping the artificial heart

As soon as both ventricles were fully primed the tourniquets around the veins were released and the aortic clamp removed. The left ventricle was pumped at low pressure and with a low pump rate. The pulmonary occlusion was then gradually and partially released, and the right ventricle was pumped at a low pressure. The right atrial pressure was maintained above zero millimeters of mercury to avoid suction of air through the anastomoses. The superior vena caval catheter was clamped and the pulmonary artery clamp was completely released. The pump pressure and rate were gradually increased as cardiopulmonary bypass flow was reduced. Finally, the inferior vena caval catheter was clamped to increase the right atrial pressure. Residual fluid in the cardiopulmonary bypass circuit was gradually infused into the animal until an

arterial mean pressure of 70 to 100 millimeters of mercury could be maintained or the right and left atrial pressures were maintained above zero millimeters of mercury. After the animal's condition was stabilized and further blood administration was unnecessary, the venous and arterial lines for cardiopulmonary bypass were removed.

5. Postpumping Procedure and Postoperative Management

Protamine sulphate was given intravenously in a dose 1.5 milligrams per milligram of heparin or until the whole blood clotting time returned to between eight and twelve minutes. The chest tubes were inserted into the pleural space. The sternum was approximated by stainless steel wire sutures and the chest was closed in two layers to obtain air-tight closure. Intermittent heavy silk sutures were used in the skin, especially in an area where the sternum might rub on the cage.

After the operation the animal was transferred to a specially constructed mobile cage and placed in the kneeling position. Respiratory assistance was continued as required in order to maintain acceptable levels of arterial oxygen saturation and an endotracheal tube was left in position until the animal was able to maintain an acceptable partial pressure of oxygen with spontaneous respiration. Intravenous fluids and blood were transfused to the animal as the situation demanded.

A urinary catheter was inserted through the urethra or operatively directed to the bladder. Two people continuously attended the needs of the animal, performing the many tests mentioned in the following section.

C. Parameters Monitored and Tests Performed

Several pressures were detected by Statham, Hatorey and Puerto Rico transducers connected to the exteriorized polyethylene catheters, eight feet in length and 0.085 inches in internal diameter. They were displayed or recorded on a six channel Beckman Dynograph. Aortic, left atrial, pulmonary arterial, right atrial and central venous pressure were monitored.

Cardiac output was determined by the dye dilution method using indocyanine-green injected into the right atrium while continuously sampling from the aorta.[14, 84]

The arterial and venous pH, pO_2 and pCO_2 were periodically determined throughout the experiment.

A pH Gas Analyzer (Model 113, Instrumentation Laboratory Inc., Lexington, Massachusetts, U.S.A.) and a Constant Temperature Bath (Model 127, Instrumentation Laboratory Inc., Boston, Mass., U.S.A.) were used for determining the blood pH, pO_2 and pCO_2. After the analyzer and the bath were stabilized, the standard buffer solutions of pH 6.84 and pH 7.384 were used to calibrate the pH electrodes.

Two gas mixtures were used to calibrate the pO_2 and pCO_2 electrodes:

1. 0% O_2, 10% CO_2
2. 12% O_2, 5% CO_2

The partial pressure of a gas is the fractional concentration (f) of that gas times the total pressure less water vapor pressure:
Partial pressure = Functional conc. x (barometric pressure - 47 mm Hg).

Water vapor pressure is 47 mm Hg at 37°C and the barometric pressure averages 700 mm Hg in Edmonton (2200 ft.), Alberta, Canada. Therefore, the partial pressures of O_2 and CO_2 were calculated by:

$$pO_2 \text{ or } pCO_2 = (FO_2 \text{ or } FCO_2)\ (653).$$

For the two calibration mixtures shown above the partial pressures were:

1. 0 mm Hg pO_2, 65.3 mm Hg pCO_2
2. 78.3 mm Hg pO_2, 32.6 mm Hg pCO_2

Plasma free hemoglobin (Shinowara's method)[76], total serum protein (Biuret reaction), serum electrolytes of Na^+, K^+, Ca^{++} and Cl^- (IL flame photometer, atomic absorption and Buchler-Cotlove Chloridometer)[37], serum lactate and pyruvate (Sigma Kit method), serum histamine (fluorescent technique)[77], hematocrit (microhematocrit method), hemoglobin level (Drabkin's method), red blood cell and white blood cell counts (Coulter counter), platelet counts (ammonium oxalate methods) and Lee-White clotting time were measured periodically. Hourly urinary output was recorded throughout the experiment.

D. Postmortem Examination

In the early experiments the animals were examined within a short time of death; in the later experiments, however, the animals were sacrificed if their condition deteriorated markedly, e.g. severe metabolic acidosis, arterial pO_2 less than 50 mm Hg (spontaneous respiration with 6 L/m nasal oxygen), poor tidal volume, or progressive diastolic hypotension. Prior to sacrifice, succinylcholine chloride (0.5 to 0.8 mg/kg) was given intravenously to avoid anoxic convulsion.

The animal was then placed on its left side and the chest opened through the previous sternotomy. While the artificial heart was kept pumping and ventilating the lungs with a respirator, the state of the heart, the condition of the lungs, and the relationship between the artificial heart and the surrounding organs were carefully observed. The heart was then stopped and the endotracheal tube was removed. The brain, lungs, liver, kidneys and spleen were macroscopically examined. Sections of these organs were taken from multiple sites for microscopic examination. Other organs were examined as the situation demanded.

CHAPTER III

RESULTS AND DISCUSSION

A. Postoperative Course

From November 1971 to November 1972, the natural heart in 22 calves was replaced with a total artificial heart. During the operation cardiopulmonary bypass was used to support the animal. Nine of these artificial hearts were of the sac-type and 13 of the diaphragm-type (Table 1).

1. General Postoperative Condition

The postoperative condition of the animals, following implantation of the artificial heart, varied considerably (Table 2).

Of the 22 animals which had an artificial heart implanted, six had good postoperative recovery. They all passed a large amount of urine, responded to environmental stimuli, attempted to stand up several times (Fig. 18, 19). Three of these six animals survived more than 30 hours with an artificial heart; the maximum survival was 33 hours.

TABLE 1

TOTAL ARTIFICIAL HEART REPLACEMENTS

- 22 REPLACEMENTS
  - 9: SAC-TYPE
  - 13: DIAPHRAGM-TYPE
    - 9: MARK IX
    - 4: MARK XII

TABLE 2

TOTAL ARTIFICIAL HEART EXPERIMENTS

Exp. No.	Heart Type	Duration of Pumping (Hrs)	Cause of Death	Comments
1	Sac	8:10	Cracking of left ventricle	Good recovery
2	Sac	0:35	Kinking of left air pipe	
3*	Sac	0:30	Acute pulmonary congestion	
4	Sac	18:25	Convulsion	
5	Sac	22:20	Convulsion	Good recovery
6	Sac	6:40	Low cardiac output	
7	Sac	33:15	Convulsion	Good recovery
8	Sac	30:40	Convulsion	Good recovery
9*	Sac	8:30	Pulmonary congestion	
10				
11	Note: Appendage			
12	replacement by means of hypothermia.			
13	Diaphragm MK IX	6:05	Low cardiac output	
14	MK IX	4:05	Sacrificed	Chest not closed
15	MK IX	4:20	Air embolism	
16	MK IX	2:10	Postoperative hemorrhage	
17	MK IX	1:30	Low cardiac output	

18	MK IX	8:00	Low cardiac output	
19	MK IX	8:00	Low cardiac output	
20	MK IX	8:45	Low cardiac output	
21*	MK IX	2:20	Acute pulmonary edema	
22	MK XII	8:20	Left air driving line dislodged	Good recovery
23	MK XII	32:50	Convulsion	Good recovery
24*	MK XII	1:00	Acute pulmonary edema	
25	MK XII	10:15	Low cardiac output	

*Sacrificed due to acute pulmonary complication.

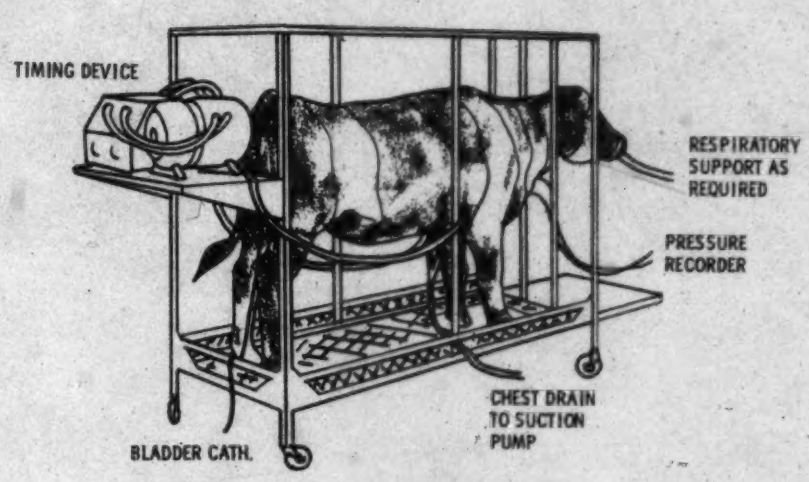

Fig. 18 Illustration of the timing device and the calf in the postoperative cage.

Fig. 19 Calf attempting to stand up in the postoperative cage.

Three of the six animals having good postoperative recovery were occasionally allowed to breath spontaneously. Nasal oxygen flowing at 3 to 4 liters per minute was given. Two other animals breathed spontaneously, with nasal oxygen, at 3 to 4 liters per minute, from approximately five hours postoperative until termination of the experiment. One other animal needed mechanically assisted respiration throughout the experiment (Bird respirator with oxygen air mixture).

Seven animals suffered from postoperative low cardiac output. Surviving up to 10 hours they maintained acceptable levels of arterial pO_2 with spontaneous respiration and nasal oxygen. However, they made no attempt to stand and were very lethargic. They only passed 500 ml to 2 liters of urine throughout the experiment and showed a gradual decrease in hourly urine output. These animals developed severe metabolic acidosis and the arterial oxygen saturation deteriorated markedly.

Six animals survived less than four hours; three of these developed acute pulmonary edema or congestion. One experiment was terminated eight and one half hours after pumping commenced due to pulmonary hypertension and low arterial oxygen saturation. This occurred even though the animal was mechanically ventilated with 100% oxygen on a Bird or Engstrom respirator.

2. Causes of Death

Low cardiac output was the most common cause of death, followed by convulsion and then by acute pulmonary complication (Fig. 20).

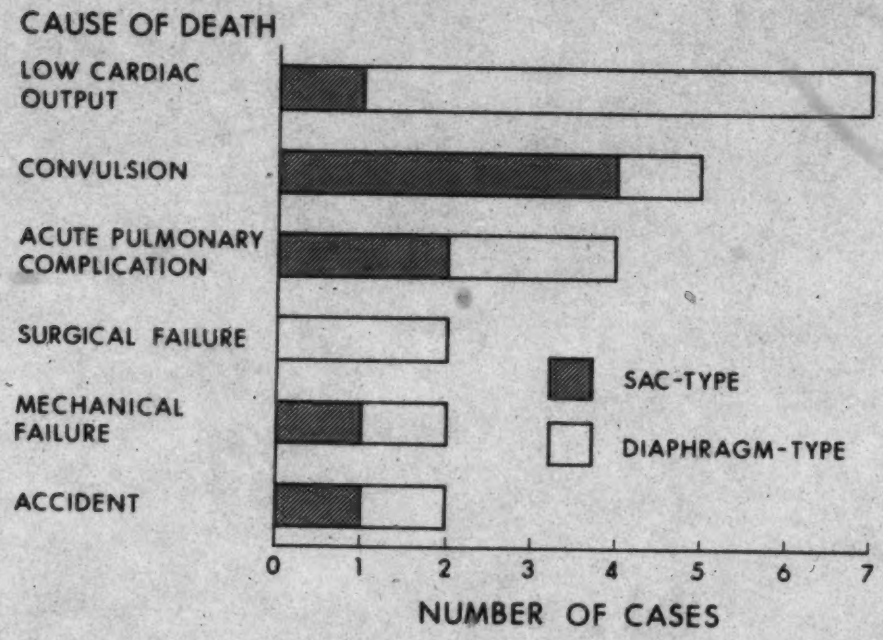

Fig. 20 Causes of death in animals with a total artificial heart.

Seven of the 22 animals died due to low cardiac output; six of these animals' hearts were replaced with a diaphragm-type artificial heart. Five animals died due to convulsion and four of these had a sac-type artificial heart implanted. Four animals died due to acute pulmonary complication; two of these animals had sac-type artificial hearts and two had diaphragm-type artificial hearts. Two animals suffered mechanical failure: one had a fracture of the left ventricle, the other an air embolism. Two animals died due to accidents: in one case kinking of the left air pipe and the other, accidental disconnection of the left air line. Two animals were sacrificed due to surgical failure: in one case excessive postoperative hemorrhage and the diaphragm-type MK IX artificial heart was much too large for the chest cavity

in the other and as a result the chest could not be closed.

Figure 21 and 22 show cause of death and the type of artificial heart placed in the animals.

Four of the nine animals with the sac-type artificial heart died due to convulsion. This was the most common cause of death with the sac-type heart. Acute pulmonary complication was also a common cause of death (Fig. 21).

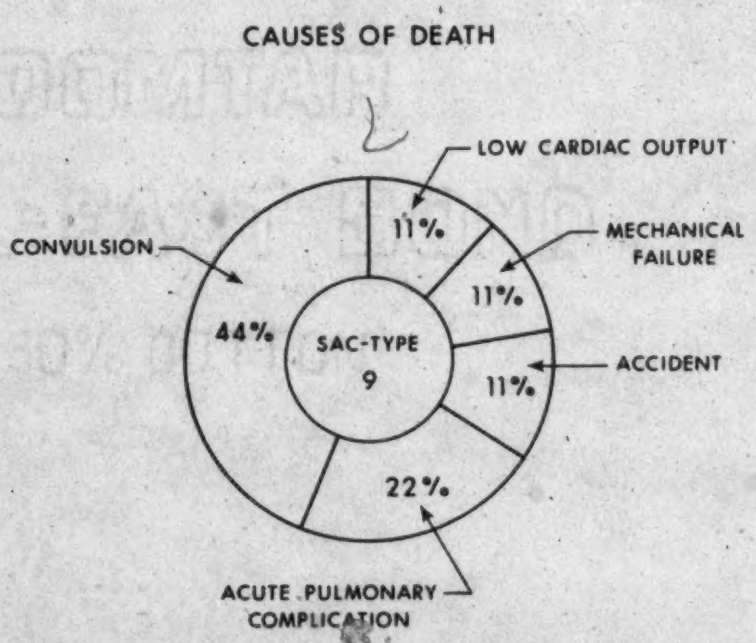

Fig. 21 Causes of death in animals with a sac-type artificial heart.

Six of the 13 animals with a diaphragm-type artificial heart died due to low cardiac output. Two animals died due to acute pulmonary complication, and two animals died due to surgical failure (Fig. 22). Acute pulmonary complication was the second most common cause of death for both types of artificial heart.

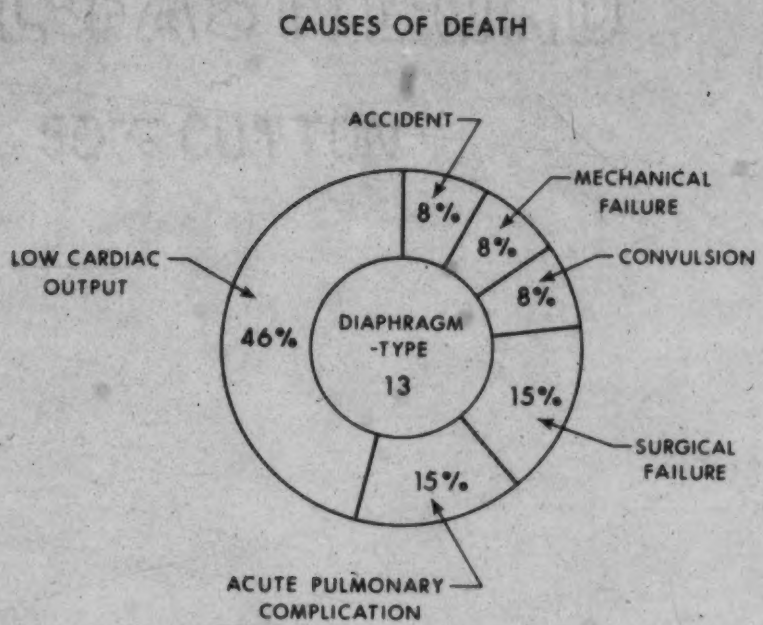

Fig. 22 Causes of death in animals with a diaphragm-type artificial heart.

Figure 23 shows cause of death and pumping time of the artificial heart.

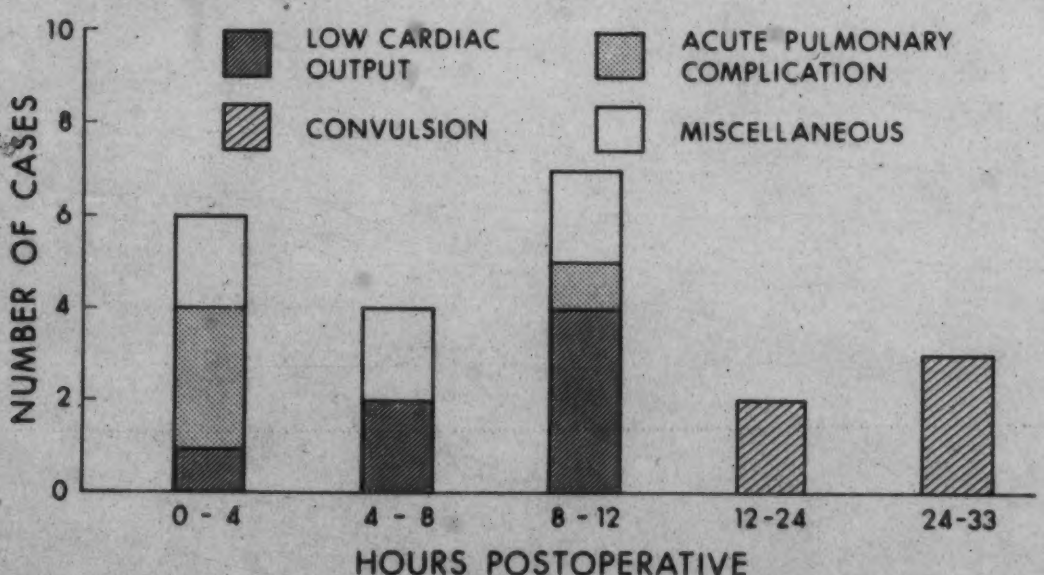

Fig. 23 Cause of death and artificial heart pumping time.

Three of six animals that died after less than four hours of pumping died due to acute pulmonary complication. This condition became evident soon after the artificial right ventricle began circulating blood through the lung, prior to closure of the chest. Animals that suffered from severe acute pulmonary edema showed a low arterial oxygen saturation and high arterial pCO_2. As a terminal event a large amount of frothy fluid was expelled through the endotracheal tube.

Death of an animal after less than 12 hours of pumping was usually caused by low cardiac output. This was seen mainly with the diaphragm-type artificial heart.

All animals that survived longer than twelve hours died as a result of convulsions. If mild convulsions gradually changed to more severe convulsions of greater frequency and duration, these animals developed metabolic acidosis, progressive diastolic hypotension and deterioration of pulmonary function. One animal that died shortly after a first major convulsion had acceptable levels of arterial pO_2 and no metabolic acidosis at the time of death.

DISCUSSION

The preoperative management of calves that were used for these experiments is very important. They are particularly susceptible to upper respiratory infection[69] and, especially in winter, some calves suffered from bronchitis. Animals that were transferred from the local stockyard, kept indoors and under supervision, proved best

for this project. We observed, however, that animals kept indoors for more than two weeks had a tendency to suffer from diarrhea.

A preoperative fasting time of less than 24 hours was generally not long enough to prevent ruminal tympany developing during the operative procedure, when the animal was in the supine position. In early experiments the animals were fasted for 12 to 18 hours. A large bore needle was used to puncture the stomach during the operation, allowing gas to escape. Gaseous distension of the abdomen compressed the inferior vena cava causing the cardiopulmonary bypass flow rate to gradually decrease. In later experiments the animals were fasted for 48 hours and it was not necessary to use needle puncture of the stomach, a peroral tube[69], or a gastrostomy[66] to allow the gas to escape. During the 48 hour fast, water and milk were allowed ad libtum, thus minimizing dehydration and loss of strength. A Holstein calf has a larger chest cavity than that of any other species and is, therefore, a good experimental model. It is also a very gentle animal.

Administration of a tranquilizer may not be necessary for premedication. However, since we have personally heard that some animals had fractured leg bones during induction of anesthesia, we recommend administration of a tranquilizer prior to induction of anesthesia.

Two different opinions regarding the inspiratory pressure and respiratory frequency for the respirator used after the calf's chest is opened have been reported[25, 49]. One recommendation is low inspiratory pressure (8 to 10 cm H_2O) and high respiratory frequency (36/min). It is believed that if the calf lung was inflated with the

same pressure as that used for the human or dog (16 to 20 cm H_2O), the damage to alveoli will cause death[[3, 48, 49]. Another recommendation is high inspiratory pressures (30 to 33 cm H_2O) and low respiratory frequency (18 to 20/min)[13, 25]. The low ventilatory pressures (15 cm H_2O or less) that were used for the early experiments probably caused the hypoxia, hypercapnea and atelectasis that developed within one hour after opening the chest. The low arterial pH was corrected at the commencement of bypass. In later experiments high pressure, large-tidal-volume ventilation (750 ml) resulted in good blood gas tensions and prevented the atelectasis.

A small functional patent ductus arteriosus was found in one animal. One animal had a functional patent foramen ovale. A patent ductus arteriosus should be ligated before commencing bypass. These defects are common in young calves, but generally close during the first few weeks of life[13].

Excessive bleeding from the atrial anastomosis has been a postoperative problem. A watertight anastomosis between the natural atrium and the rigid atrial graft was frequently difficult to achieve. The mechanical heart limited access to the anastomotic site in the narrow operative field. When the separate atrial silastic cuff was used, bleeding from the atrial anastomosis ceased to be a problem. Oozing from several sites occurred when cardiopulmonary bypass was employed for more than 90 minutes. In order to minimize this, as much dissection as possible was performed prior to administration of heparin.

The low cardiac output syndrome is one of the most difficult

problems to overcome. The cardiac output of our prosthetic heart is mainly controlled by venous return. Animals that showed good recovery after replacement of their natural heart with an artificial heart, and survived more than 12 hours, had a maximum cardiac output of 60 to 70 ml/kg/min throughout the experiment. All but one of these suffered from a minor degree of low cardiac output. Most animals with the diaphragm-type MK IX artificial heart suffered from a major degree of low cardiac output. This was caused by poor venous return due to compression of the inferior vena cava and was a result of the large size, heavy weight, and angular shape of the heart[64]. An ideal prosthetic heart should be the same weight as a natural heart and should be contained within the natural pericardium.

All animals that were spared acute pulmonary complication, accidental death, mechanical failure or low cardiac output, finally succumbed as a result of convulsions brought on by thromboembolism. Postmortem examination revealed that the prebiolized natural rubber sac-type artificial heart formed large thrombi at the bottom of the ventricles. However, the diaphragm-type artificial heart, which had the inside of the ventricles coated with a thin film of silicone rubber, formed fibrin thrombi at the junction between the chamber and the silastic diaphragm. Material coated with monomolecular layered undenatured albumin[53], treated by aldehyde[65], or coated over with plastic material has proved to be too thrombogenic to be used in the artificial heart. The surface of a ventricle which has Dacron fibrils coated with fetal fibroblasts proved to have reasonable antithrombogenicity[31, 46].

Most mechanical failures and accidents are preventable.

Acute pulmonary complication after the termination of cardiopulmonary bypass and employment of a total artificial heart is a strange type of pulmonary insufficiency and many animals suffered from it, with varying degrees of severity. In animals that did not suffer severe acute pulmonary complication and had good postoperative recovery, the pulmonary function gradually deteriorated as the pumping time increased until they could no longer support themselves with spontaneous respiration.

The details of acute pulmonary complication are described and discussed in the following pages.

B. Pulmonary Complication in the Acute Phase

This section describes and discusses the postoperative changes in pulmonary arterial pressure, systemic arterial pressure and arterial blood gas examinations during the acute phase. The acute phase begins at commencement of artificial heart pumping and ends after four hours of pumping. During this period all animals were mechanically ventilated. Histological findings of the lungs from the animals that died in this period due to various causes are also described.

Twenty of 22 animals had the pulmonary arterial pressure monitored in the postoperative period. Nine of these animals had a sac-type artificial heart and 11 animals had a diaphragm-type artificial heart. In an attempt to diminish postoperative pulmonary complication five animals were treated with Methylprednisolone. One of these animals had a sac-type artificial heart and four had a diaphragm-type artificial

heart. A total of two grams of Methylprednisolone, given in four equal doses, were administered at fixed periods during the operation. The first dose was given after establishment of the venous cutdown; the second was given just prior to going on partial bypass; the third was given just after going on total bypass; the last dose was given just prior to termination of bypass.

1. Postoperative Pulmonary Arterial Pressure

In five animals the mean pulmonary arterial pressure (PAP) was measured by inserting a catheter via the left jugular vein before the chest was opened. The normal PAP of calves was between 10 and 20 mm Hg.

Table 3 shows the postoperative maximum PAP, the duration of PAP higher than 30 mm Hg, the total cardiopulmonary bypass time, the mean systemic arterial pressure at the time of maximum PAP, and the type of artificial heart placed in the animals.

Most animals developed a maximum PAP between 40 and 65 mm Hg after pumping with the artificial heart. Three animals developed a maximum PAP higher than 70 mm Hg and two of these animals were sacrificed due to acute pulmonary complication. Two animals that underwent total cardiopulmonary bypass for more than 100 minutes were sacrificed due to acute pulmonary edema after less than two hours of pumping. Thus, fatal acute pulmonary complications develop in animals that either have a prolonged cardiopulmonary bypass (greater than 100 minutes), or develop a high postoperative PAP (greater than 70 mm Hg).

TABLE 3

POSTOPERATIVE BLOOD PRESSURES AND BYPASS DURATION

Exp No	Max PAP (mm Hg)	PAP>30 (min)	CPB (min)	SAP (mm Hg)	Heart Type	Comments
1	60	40	77	100/60	Sac	
2	60	*	75	80/40	Sac	
3**	75	*	60	50/30	Sac	
4	60	40	62	80/40	Sac	
5	35	5	62	80/40	Sac	
6	35	15	69	60/20	Sac	
7	45	135	73	100/80	Sac	
8	40	45	81	100/80	Sac	MPS
9**	70	*(510)	62	90/30	Sac	
10-12	Note: Appendage. Replaced by hypothermia					
13	45	20	78	100/40	MK IX	
14	65	40	84	90/38	MK IX	
15	55	*(260)	75	100/60	MK IX	
16	60	125	87	70/40	MK IX	
17	75	80	79	120/50	MK IX	
18	55	150	63	60/40	MK IX	
19	57	80	63	60/40	MK IX	
20	28	0	90	100/40	MK IX	MPS
21**	50	30	110	90/50	MK IX	MPS
22	40	25	76	85/55	MK XII	MPS
23	-	-	70	120/50	MK XII	MPS
24**	-	-	110	80/34	MK XII	
25	40	20	72	100/20	MK XII	MPS

* Throughout the experiment
** Sacrificed due to acute pulmonary complication
\- No monitoring
PAP - Pulmonary arterial pressure
CPB - Total cardiopulmonary bypass time
SAP - Systemic arterial pressure at the time of maximum PAP
MPS - Treated with Methylprednisolone

There was no relation between the postoperative maximum PAP and the duration of total cardiopulmonary bypass. Neither was there any relation between the postoperative maximum PAP and the type of artificial heart used. All the animals treated with Methylprednisolone showed a postoperative maximum PAP of less than 55 mm Hg (Fig. 24).

The duration of PAP higher than 30 mm Hg varied considerably (Fig. 25). In 11 of 20 animals the PAP decreased to less than 30 mm Hg before one hour of pumping. Two animals maintained a PAP higher than 30 mm Hg for one to two hours of pumping. In two other animals the PAP was higher than 30 mm Hg for more than four hours of pumping. The PAP in five animals treated with Methylprednisolone decreased to less than 30 mm Hg within an hour after the onset of pumping by the artificial heart. Two animals were sacrificed, one due to severe acute pulmonary complication and one after an accident, before the PAP had decreased to less than 30 mm Hg.

The time course of the postoperative PAP varied with the type of artificial heart and administration of Methylprednisolone. The animals are divided into three groups: sac-type artificial heart group, diaphragm-type artificial heart, and Methylprednisolone group (regardless of type of artificial heart).

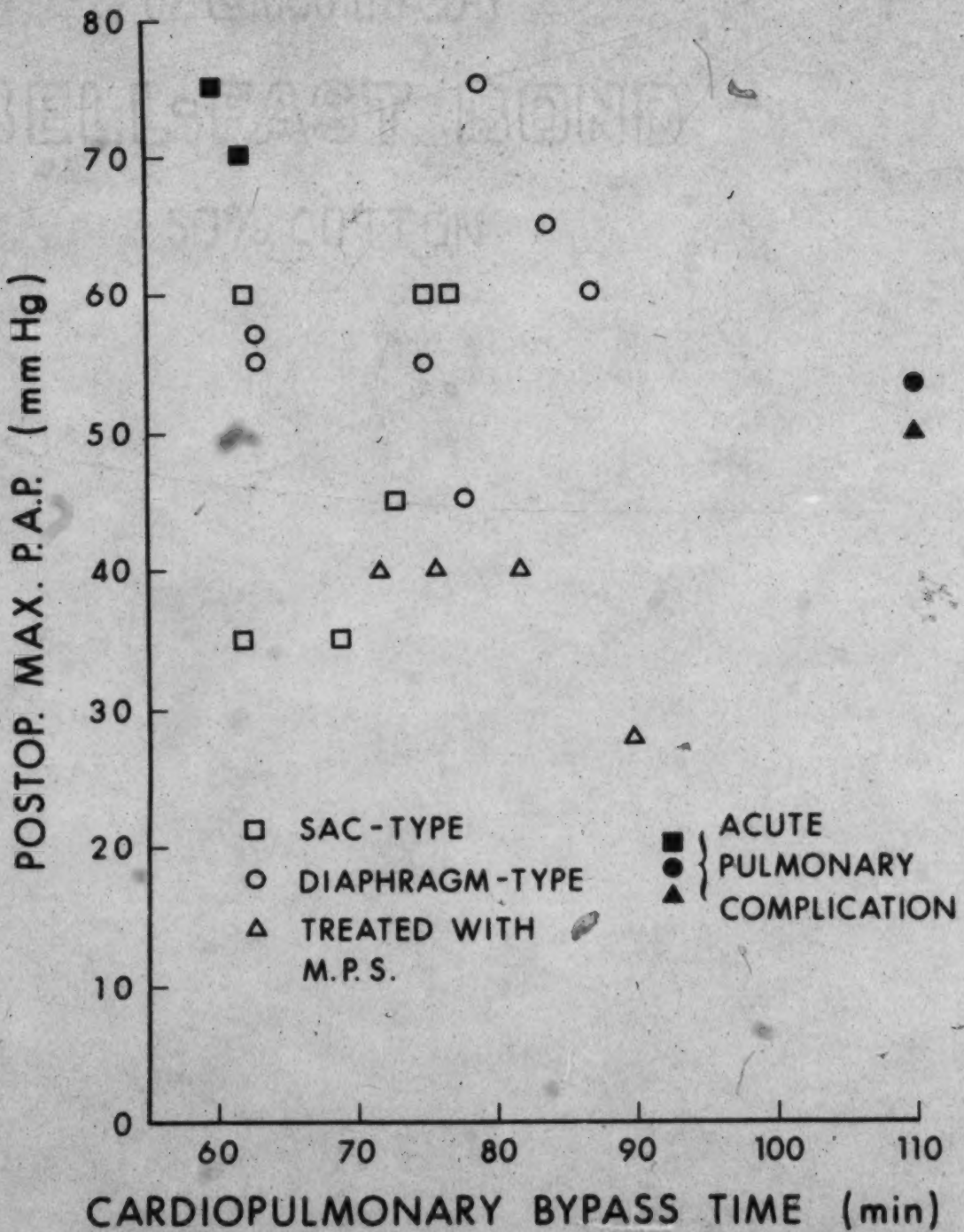

Fig. 24 The postoperative maximum pulmonary arterial pressure and the duration of total cardiopulmonary bypass for each type of artificial heart used.

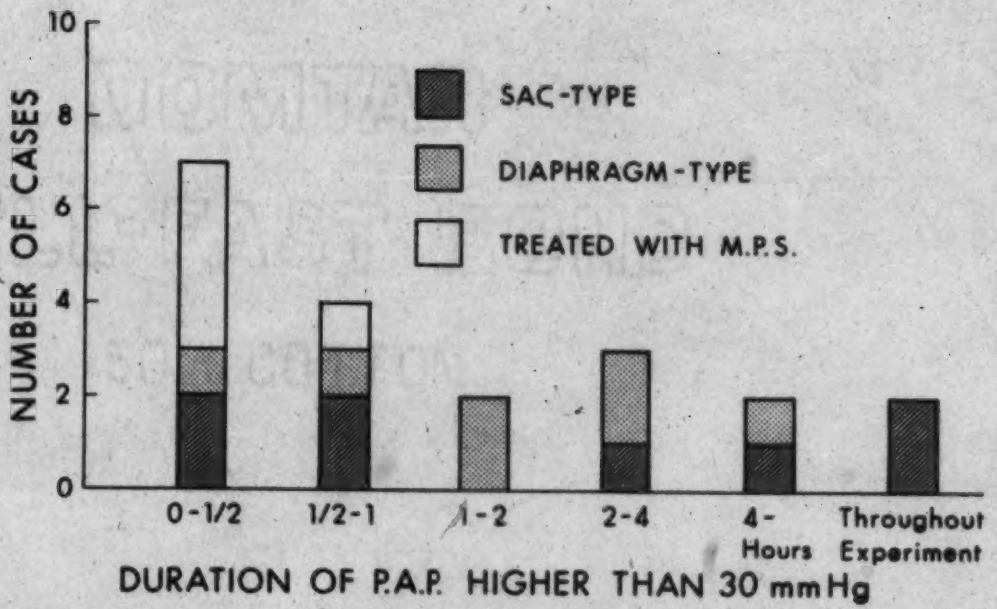

Fig. 25 The duration of elevated pulmonary arterial pressure for each group.

a. Sac-type artificial heart group

Table 4 shows the postoperative PAP of each animal. Three of eight animals showed a maximum PAP between 35 and 75 mm Hg immediately after pumping commenced. Four animals showed a maximum PAP between 35 and 60 mm Hg after five minutes of pumping. In one animal the PAP increased gradually to a maximum of 70 mm Hg after 20 minutes of pumping and during the following 15 minutes the PAP decreased gradually to between 35 and 45 mm Hg. In most animals the PAP decreased to less than 30 mm Hg after 40 minutes of pumping. One animal still maintained a PAP higher than 40 mm Hg after three hours of pumping and this resulted in poor pulmonary function. In the one animal in which the left air driving line was kinked 28 minutes after pumping began, the PAP rose to 50 mm Hg in the next ten minutes. Because we were unaware of this kinking, the right ventricle continued to be driven as usual. One animal showed a maximum PAP of 75 mm Hg and expelled a large amount of frothy fluid through the endotracheal tube; its PAP was 60 mm Hg at the termination of the experiment.

b. Diaphragm-type artificial heart group

In this series the postoperative condition of each animal was more varied than that of the animals in the sac-type artificial heart group. Table 5 shows the postoperative PAP of each animal Two of seven animals showed a maximum PAP of between 60 and 75 mm Hg immediately after pumping commenced. Three animals showed a maximum level of 55 mm Hg after approximately 15 minutes of pumping. In most animals the PAP decreased slowly in 30 minutes from its maximum to between 40 and 55 mm Hg. After an hour of pumping five of seven animals

TABLE 4

POSTOPERATIVE MEAN PULMONARY ARTERIAL PRESSURE FOLLOWING TOTAL SAC-TYPE ARTIFICIAL HEART REPLACEMENT

	Mean Pulmonary Arterial Pressure (mm Hg)										
Exp. No.	0	5	10	20	30	40	60	90	120	150	180 (min)
1	50	60	50	35	30	28					
2*	32	60	34	32	45	50					
3†	75	68	60	50	65						
4	45	60	50	45	40	28					
5	35	30	25								
6	32	35	35	25							
7	45	40	44	35	35	34	32	32	32	28	
9†	65	60	65	70	68	65	55	47	44	42	42
Mean Value	47	51	45	39	37	34	28				

*Kink in the left air line

†Sacrificed due to acute pulmonary complication

Zero time is when the artificial heart begins pumping.

TABLE 5

POSTOPERATIVE MEAN PULMONARY ARTERIAL PRESSURE FOLLOWING TOTAL DIAPHRAGM-TYPE ARTIFICIAL HEART REPLACEMENT

Exp. No.	Time min.	Mean Pulmonary Arterial Pressure (mm Hg)										
		0	5	10	20	30	40	60	90	120	150	180
13		32	45	34	28							
14		60	65	54	50	38	28					
15		40	40	55	55	55	52	48	44	42	40	40
16		60	56	50	52	44	43	42	38	32		
17		75	50	45	50	40	32	44	30			
18		50	54	48	48	48	48	48	44	35	30	
19		42	45	50	57	56	54	46	28			
Mean Value		50	51	48	48	44	40	39	33	29		

maintained a PAP higher than 40 mm Hg and the other two animals had a PAP of less than 30 mm Hg.

c. The treated group

One of the five animals treated with Methylprednisolone had a sac-type artificial heart and four others had diaphragm-type artificial hearts. Table 6 shows the postoperative PAP for each animal. Four of the five animals showed a maximum PAP between 28 and 50 mm Hg immediately after commencement of pumping. In the other animal the PAP reached a maximum level of approximately 40 mm Hg after five minutes of pumping and stayed at this level for the following 30 minutes. In four of five animals the PAP decreased rapidly to less than 30 mm Hg before 30 minutes of pumping. The other animal had a PAP higher than 30 mm Hg until 40 minutes of pumping.

d. Group mean PAP - time course for each group

The mean values of the postoperative PAP were calculated statistically for each group. These are shown in Figure 26.

In the treated group both maximum postoperative PAP and the duration of PAP higher than 30 mm Hg were much less than those in the other groups. In these groups, immediately after pumping commenced, the PAP was maximum at 38 mm Hg and then decreased gradually to less than 30 mm Hg by 30 minutes of pumping. In the sac-type and diaphragm-type artificial heart groups the PAP reached a maximum of 51 mm Hg after five minutes of pumping. In the sac-type artificial heart group the PAP decreased rapidly to 37 mm Hg during the following 15 minutes and then gradually decreased to less than 30 mm Hg after 60 minutes of

TABLE 6

POSTOPERATIVE MEAN PULMONARY ARTERIAL PRESSURE IN THE ANIMALS TREATED WITH METHYLPREDNISOLONE FOLLOWING TOTAL ARTIFICIAL HEART REPLACEMENT

Exp. No.	Mean Pulmonary Arterial Pressure (mm Hg)							Type of Heart
Time min.	0	5	10	20	30	40	60	
8	30	40	39	39	40	30	28	Sac
20	38	26	25	25	21			Diaph MK IX
21*	50	40	35	34	30			Diaph MK IX
22	40	32	32	28	22			Diaph MK XII
25	40	34	34	28	23			Diaph MK XII
Mean Value	38	34	33	31	27			

*Sacrificed due to acute pulmonary complication

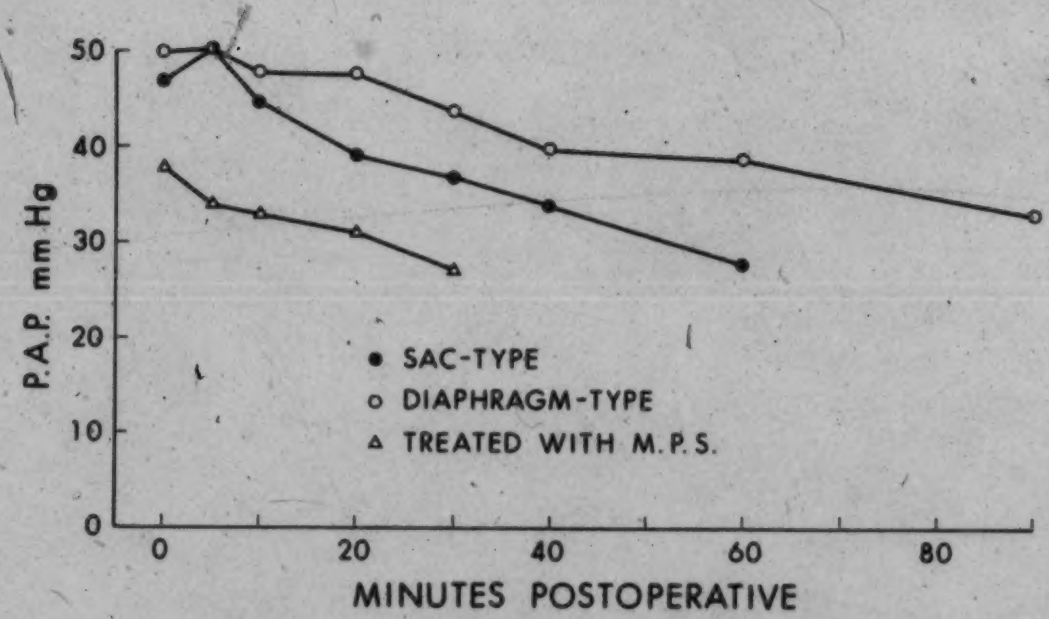

Fig. 26 Postoperative pulmonary arterial pressure for each group.

MPS : Methylprednisolone

pumping. In the diaphragm-type artificial heart group the PAP decreased gradually to 40 mm Hg over 30 minutes and then slowly decreased to 30 mm Hg after two hours of pumping.

2. Postoperative Systemic Arterial Pressure

The systemic arterial pressure was monitored continuously and recorded throughout the experiments. The arterial and venous pH, pO_2 and pCO_2 were determined periodically. Nine animals had a sac-type artificial heart and one of these animals was treated with Methylprednisolone. Thirteen animals had a diaphragm-type artificial heart and five of them were treated with Methylprednisolone. After pumping commenced the animal was mechanically ventilated with 100% oxygen. Closure of the chest was started after about one hour of pumping and the chest was completely closed in the following hour. In the acute phase all 22 animals were mechanically ventilated. The mean systemic arterial pressures (SAP), the arterial pH, pO_2 and pCO_2 are classified and described by group.

a. Sac-type artificial heart group

Table 7 shows the postoperative SAP of each animal.

Immediately after pumping commenced, most animals showed a SAP between 35 and 55 mm Hg. By 10 minutes of pumping the SAP was higher than 60 mm Hg and after 30 minutes it stabilized between 60 and 80 mm Hg. Once the chest was closed and the animal was placed in the kneeling position, the SAP increased further to between 70 and

TABLE 7

POSTOPERATIVE MEAN SYSTEMIC ARTERIAL PRESSURE FOLLOWING TOTAL SAC-TYPE ARTIFICIAL HEART REPLACEMENT

Exp. No.	Mean Systemic Arterial Pressure (mm Hg)									
Time min.	0	5	10	20	30	40	60	90	120	150
1	50	50	88	70	65	72	66	64	64	80
2*	38	40	60	60	62	38				
3**	38	40	50	40	36					
4	40	56	60	60	60	60	58	60	80	82
5	40	50	64	64	62	70	56	58	68	66
6	30	30	38	50	42	30	36	32	46	54
7	58	70	76	76	98	70	64	70	70	80
9**	36	40	42	36	50	48	60	80	108	92
Mean value	41	47	60	57	62	61	57	61	73	76

*Accidental kinking of left air driving line

**Sacrificed due to acute pulmonary complication

90 mm Hg.

Two of eight animals were sacrificed after approximately 40 minutes of pumping. The animal with acute pulmonary complication showed a SAP of about 40 mm Hg. The animal that suffered from kinking of the left air pipe maintained a SAP at 60 mm Hg until five minutes following the accident. Then the SAP decreased rapidly from 62 to 38 mm Hg, the left atrial pressure increased from 5 mm Hg to higher than 30 mm Hg, and the right atrial pressure decreased from 3 to -2 mm Hg.

b. Diaphragm-type artificial heart group

Table 8 shows the postoperative SAP of each animal.

Immediately after pumping most of the animals showed a SAP between 40 and 50 mm Hg and after 10 minutes of pumping the SAP increased to between 50 and 70 mm Hg and stabilized. However, after approximately one and a half hours of pumping, when closure of the chest was begun, most of the animals suffered from low cardiac output due to compression of the inferior vena cava by the right artificial ventricle. In one animal that suffered severely from low cardiac output, the SAP decreased rapidly from 70 to 24 mm Hg after closure of the chest. Before the chest was closed the right atrial pressure was 2 mm Hg with an inferior vena caval pressure of 3 mm Hg. During closure of the chest the right atrial pressure decreased to -2 mm Hg and the inferior vena caval pressure increased to 5 mm Hg. The pressure gradient between the right atrium and the inferior vena cava was 10 mm Hg just before sacrifice.

Three of the eight animals were sacrificed before two hours of pumping had been completed. One died from postoperative hemorrhage,

TABLE 8

POSTOPERATIVE MEAN SYSTEMIC ARTERIAL PRESSURE FOLLOWING TOTAL DIAPHRAGM-TYPE ARTIFICIAL HEART REPLACEMENT

Exp. No.	Mean Systemic Arterial Pressure (mm Hg)									
Time min	0	5	10	20	30	40	60	90	120	150
13	45	45	50	68	62	62	63	78	84	74
14	40	60	64	70	66	64	52	42	42	58
15	44	62	70	70	80	60	80	60	58	74
16	30	48	78	44	46	64	42	32	30	
17	42	82	66	73	68	70	62	24		
18	38	38	36	48	46	44	50	54	52	66
19	52	54	52	42	40	68	58	54	52	66
24*	48	50	52	54	52	52	50			
Mean value	42	55	59	59	58	58	57	49	45	

*Sacrificed due to acute pulmonary complication

another died from low cardiac output and the third died from acute pulmonary complication.

c. The treated group

Table 9 shows the postoperative SAP of each animal. Immediately after pumping most animals showed the SAP approximately 60 mm Hg. After 10 minutes of pumping, in three of six animals it increased to approximately 80 mm Hg. In three others it decreased slightly and stayed between 54 and 58 mm Hg. After an hour of pumping four animals maintained SAP between 80 and 90 mm Hg; in two others it was 60 mm Hg. After the chest was closed and the animal placed in the kneeling position, four animals that had a sac-type or a diaphragm-type MK XII artificial heart showed a further SAP increase of between 80 and 100 mm Hg. However the SAP decreased rapidly in two animals that had a diaphragm-type MK IX artificial heart.

d. Group mean systemic arterial pressure - time course for each group

The mean value of the postoperative SAP was calculated statistically for each group. The results are shown in Figure 27.

In both sac-type and diaphragm-type artificial heart groups the mean systemic arterial pressure reach approximately 60 mm Hg about 15 minutes after pumping commenced. After the chest was closed and the animal placed in the kneeling position, the sac-type artificial heart group showed a SAP increase to 80 mm Hg. In the diaphragm-type artificial heart group it decreased rapidly to 40 mm Hg due to compression of the inferior vena cava by the artificial heart. In the treated group the SAP was maintained higher than 60 mm Hg immediately

TABLE 9

POSTOPERATIVE MEAN SYSTEMIC ARTERIAL PRESSURE IN THE ANIMALS TREATED WITH METHYLPREDNISOLONE FOLLOWING TOTAL ARTIFICIAL HEART REPLACEMENT

Exp. No.	Mean Systémic Arterial Pressure (mm Hg)										Type of Heart
	Time min.	0	5	10	20	30	40	60	90	120	150
8		60	80	80	80	82	86	86	90	102	100	Sac
20		62	64	54	58	64	62	58	38	46	48	Diaph MK IX
21*		62	58	58	56	52	74	80	52	30	28	Diaph MK IX
22		60	58	58	56	52	52	62	92	90	80	MK XII
23		60	70	76	80	80	78	75	75	75	80	MK XII
25		56	58	74	74	78	78	82	78	76	74	MK XII
Mean value		60	65	67	67	68	71	74	71	70	68	

*Sacrificed due to acute pulmonary complication

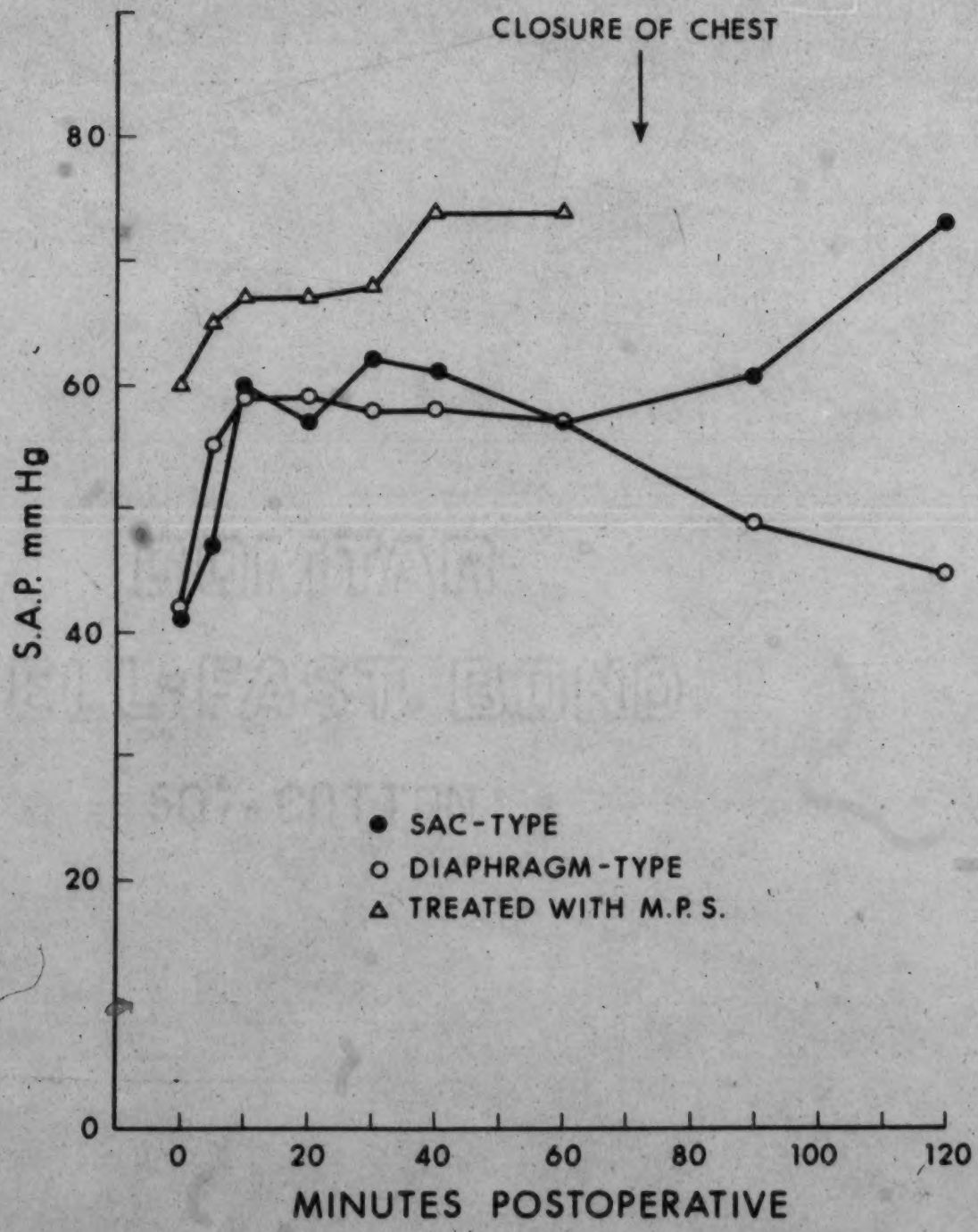

Fig. 27 Postoperative systemic arterial pressure for each group.

after pumping and then increased gradually to 80 mm Hg. However, after closure of the chest was begun, the changes of the SAP were dependent upon the type of artificial heart used.

In four animals that were sacrificed due to severe acute pulmonary complication, the SAP was lower than that of the other animals after pumping commenced (Table 7, 8 and 9).

3. Postmortem Pathological Examination of the Lungs

Eight of 22 animals were sacrificed or died in the acute phase. One animal was mechanically ventilated throughout the experiment and sacrificed due to severe acute pulmonary complication after eight hours of pumping.

This section describes the pathological findings of the lungs from these nine animals.

Four of these nine animals suffered from severe acute pulmonary complication. Five animals were sacrificed due to various causes: kinking of the left air pipe, inability to close the chest due to the small chest cavity, air embolism, postoperative hemorrhage and acute low cardiac output.

In all animals acute passive congestion was observed in the dorsal parts of the lower lobes of the lungs during and after cardiopulmonary bypass. The upper and middle lobes did not suffer from this congestion. When cardiopulmonary bypass was longer than 80 minutes, the interlobular spaces were widened and interlobular edema

was macroscopically observed in the dorsal parts of the lower lobes at termination of the bypass. As soon as the pulmonary circulation was restored (pumping with an artificial heart) the acute passive congestion disappeared quickly, while the interlobular edema disappeared slowly.

If bypass lasted for more than 110 minutes, further congestion and edema developed (Fig. 28) and copious frothy fluid was expelled through the endotracheal tube after about two hours of pumping.

Fig. 28 The lung from an animal after 110 minutes of cardiopulmonary bypass and 2 hours of artificial heart pumping. Note the marked degree of edematous congestion.

These nine animals are divided into two groups: one group died due to acute pulmonary complication; the other group died from various causes in the acute postoperative phase.

a. Death due to acute pulmonary complication

Three of four animals were sacrificed due to acute pulmonary complication after less than two hours of pumping, while one animal was sacrificed after eight hours of pumping. Table 10 shows macroscopic and microscopic findings in the lungs.

Two animals had a mean pulmonary arterial pressure higher than 70 mm Hg after pumping began. One of these suffered from rapid pulmonary congestion after the start of pumping. Acute passive congestion in the dorsal parts of the lower lobes disappeared immediately after pumping began, but when the PAP reached 70 mm Hg after five minutes of pumping, the entire lungs were seriously congested once again. After 30 minutes of pumping copious frothy fluid was expelled through the endotracheal tube. At the postmortem examination the lungs showed dominant congestion and moderate edema. Intra-alveolar hemorrhage and edema were seen in the lobes of the lungs (Fig. 29).

The other animal was mechanically ventilated throughout the experiment. Before the chest was closed the whole of both lungs was moderately congested, but gross edema was not seen. After eight hours of pumping copious bloody frothy fluid flowed through the endotracheal tube. The entire lungs showed a marked degree of edematous congestion and there was atelectasis in the lower lobes. Interlobular and intra-alveolar edema and hemorrhage were seen under the microscope (Fig. 30).

TABLE 10

PATHOLOGICAL FINDINGS IN THE LUNGS FROM THE ANIMALS THAT DIED DUE TO ACUTE PULMONARY COMPLICATION

Exp. No.	Heart Type	Duration of Pumping (hrs. min)	Findings of the lungs		Comments
			Macro	Micro	
3	Sac	0:30	Marked degree of congestion	Congestion Interlobular hemorrhage	Max PAP 75 mm Hg
9	Sac	8:30	Marked degree of congestion	Intra-alveolar and interlobular hemorrhage	Max PAP 70 mm Hg
21	MK IX	2:20	Marked degree of edema and congestion	Edema Perivascular hemorrhage	Bypass time 110 minutes
24	MK XII	1:00	Marked degree of edema and congestion	Inter- and intra-alveolar edema	Bypass time 110 min

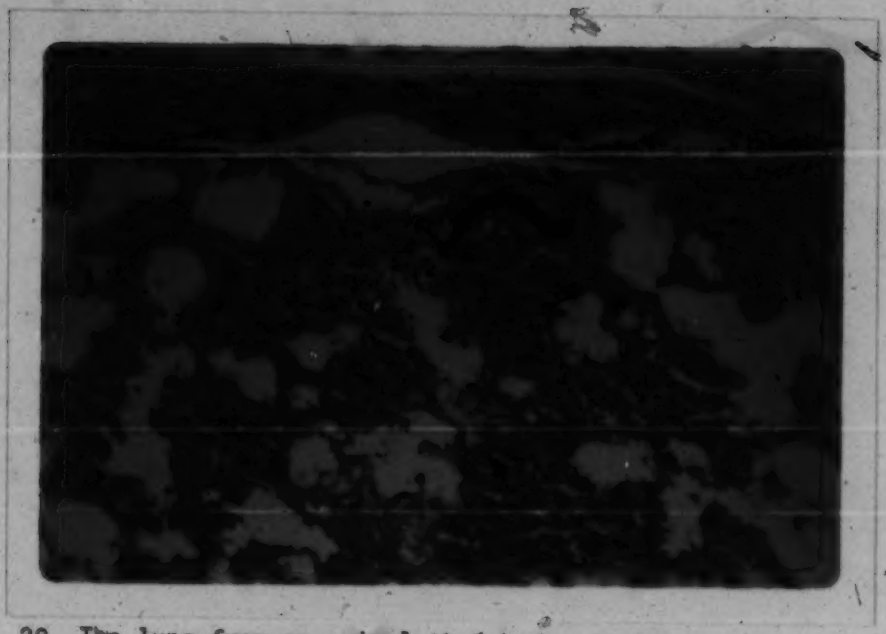

Fig. 29 The lung from an animal that had a maximum pulmonary arterial pressure of 75 mm Hg (sacrificed after 30 minutes of artificial heart pumping). Note the marked intra-alveolar hemorrhage. (H.E. x 50)

Fig. 30 The lung from an animal that had a maximum pulmonary arterial pressure of 70 mm Hg (sacrificed after 8 hours of artificial heart pumping). Note the marked degree of interlobular edema, intra-alveolar hemorrhage and edema. (H.E. x 50)

The other two animals underwent cardiopulmonary bypass for 110 minutes. Marked interlobular edema developed near the termination of bypass. Shortly after pumping began even more edema developed and was accompanied by congestion in the whole of the lungs. Interlobular spaces were seen to be markedly widened by edema. Intra-alveolar edema and hemorrhage was observed. (Fig. 31) Perivascular hemorrhage was seen under the microscope in the lungs from the animal with a diaphragm-type MK IX artificial heart.

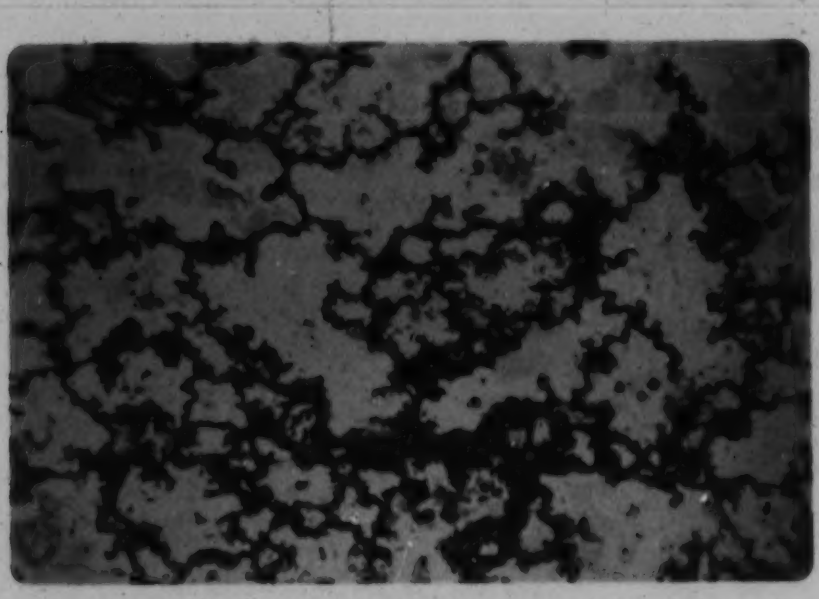

Fig. 31 The lung from an animal after 110 minutes of cardiopulmonary bypass and 2 hours of artificial heart pumping. Note the intra-alveolar edema. (H.E. x 100)

Generally, the lungs from the animals that suffered from fatal acute pulmonary complication showed a marked degree of edematous congestion. Congestion, edema and hemorrhage were seen in the whole of the lungs.

It is possible to make the following observations:

(1) In the lungs from animals that had a PAP higher than 70 mm Hg postoperatively, congestion was dominant.

(2) In the lungs from animals that underwent cardiopulmonary bypass for approximately two hours, edema was dominant.

b. Death in the acute phase

Five animals were sacrificed or died due to various causes before four hours of pumping. Table 11 shows the findings in the lungs.

One animal died accidently after 28 minutes of pumping due to a kink in the left air-driving line. These lungs showed the greatest degree of congestion; viewed microscopically, severe congestion and dilated vessels were seen in the whole of the lung.

In the animal whose chest could not be closed because of the small chest cavity compared with the heart size (diaphragm-type MK IX artificial heart) deterioration of the lungs was observed throughout the experiment. As metabolic acidosis progressed, the lungs developed edema and congestion. Intra-alveolar edema, interlobular hemorrhage, and perivascular hemorrhage were seen on microscopic examination.

In the animal that died due to air embolism moderate congestion was seen in the left lower lobe, while in all other lobes such congestion was slight. Subpleural hemorrhage was seen in those parts of the lungs which were compressed by the artificial ventricles (Fig. 32). Microscopic perivascular hemorrhage was seen in sections of the lungs.

In the animal that suffered from severe postoperative hemorrhage, moderate edematous congestion was observed in the whole of the lungs.

TABLE 11

PATHOLOGICAL FINDINGS IN THE LUNGS FROM ANIMALS THAT DIED WITHIN 4 HOURS FROM START OF ARTIFICIAL HEART PUMPING

Exp. No.	Heart Type	Duration of pumping (hrs. min)	Cause of Death	Findings of Lungs	
				Macro	Micro
2	Sac	0:35	Left ventricular air drive kinked	Marked degree of congestion	Dilation of entire pulmonary vascular bed
14	MK IX	4:05	Chest not closed	Edema, Congestion	Perivascular hemorrhage
15	MK IX	4:20	Air embolism	Slight congestion	Edema, perivascular hemorrhage
16	MK IX	2:10	Hemorrhage	Moderate edema, congestion	Intra-alveolar hemorrhage
17	MK IX	1:30	Low cardiac output	Marked degree of edema	Perivascular hemorrhage

On section of the lungs there was much frothy fluid in the respiratory tract. Microscopic examination showed edema in alveoli and interlobular spaces.

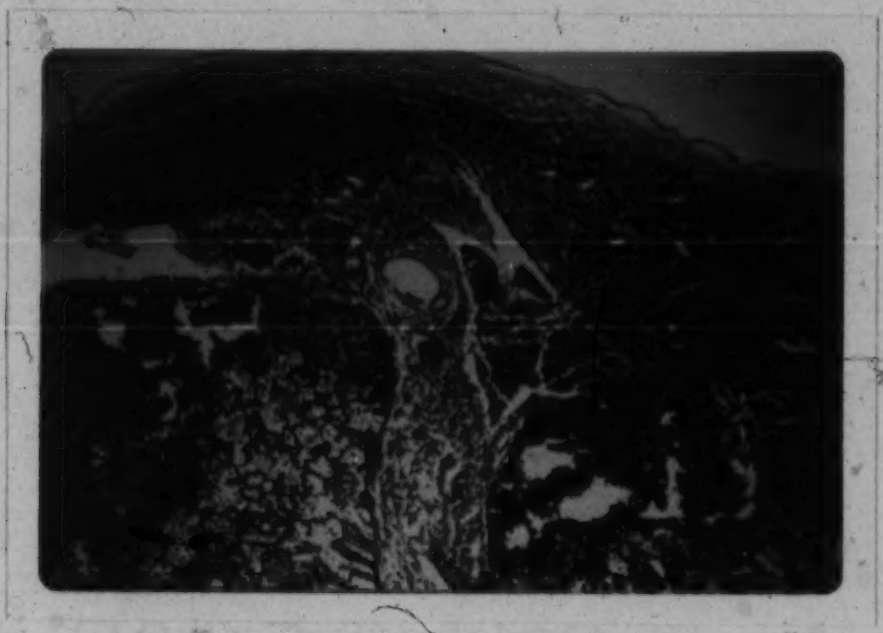

Fig. 32 The lung which was mechanically compressed by artificial heart. Note the subpleural and intra-alveolar hemorrhage. (H.E. x 50)

One animal was sacrificed after 30 minutes of severe low cardiac output caused by compression of the inferior vena cava by the right artificial ventricle. Before the chest was closed the lungs looked normal; however, at postmortem (conducted 10 minutes after the chest was closed) both lungs showed a marked degree of edema. Intra-alveolar edema, interlobular edema and perivascular hemorrhage were seen under the microscope. (Fig. 32)

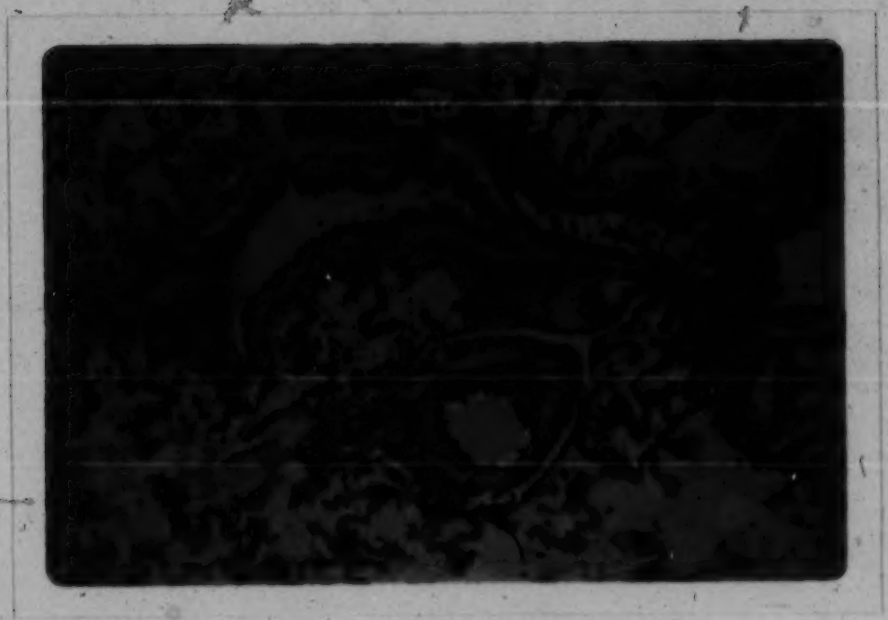

Fig. 33 The lung from an animal that suffered from low cardiac output (sacrificed after 4 hours of a MK IX artificial heart pumping). Note the marked intra-alveolar edema and perivascular hemorrhage. (H.E. x 100)

These results can be summarized as follows:

(1) The lungs from the animals that suffered from low cardiac output developed congestion and edema.

(2) Perivascular hemorrhage was seen in the lungs from animals with a diaphragm-type MK IX artificial heart.

DISCUSSION

When cardiopulmonary bypass was used for insertion of an artificial heart, almost all the calves developed pulmonary complication of various degree of severity immediately after pumping commenced. In our series of cardiopulmonary bypass control the macroscopic deterioration of the lungs was first observed in the dorsal part of the lower lobes during bypass. The calf's chest has a different shape from that of a human[66].

The chest cavity is narrow and deep, and the inferior vena cava is midway in the anterior-posterior plane. The supine position during surgery is most unphysiologic. In this position the major portion of the lungs are below the level of the vena cava; the most dependent part is as low as 15 cm below the vena cava. Acute passive congestion of the dorsal part of the lower lobes of the lungs is thus unavoidable in this position, especially during cardiopulmonary bypass. After termination of bypass most of the control calves showed temporary pulmonary hypertension (40 and 50 mm Hg) and for approximately 30 minutes after bypass the mean pulmonary arterial pressure was higher than 30 mm Hg. Therefore, the pulmonary hypertension and the histological deterioration of the lungs which occurred in calves immediately after commencement of pumping are thought to be the post-perfusion pulmonary syndrome.[26,75,78,81]

Unphysiological pressure wave patterns generated by the artificial right ventricle may contribute to this problem. Pulmonary complication develops if the output of the right ventricle exceeds that of the left. The effects of these pressure wave patterns were not analysed in detail.

The methods of ventilation after opening of the chest contributed to the severity of post-perfusion pulmonary complications in some calves. After the chest was opened most of the animals were mechanically ventilated with high pressure and a large tidal volume.[13,25] Some animals, both controls and total artificial heart replacements, were manually ventilated until starting cardiopulmonary bypass. The animals that were manually ventilated seemed to be in better pulmonary condition after bypass than those ventilated mechanically.

One of the primary surgical problems is cardiopulmonary bypass

time. When cardiopulmonary bypass exceeds 80 minutes, the chances for recovery rapidly diminish[69]. In the lungs from the animals that underwent bypass for more than 80 minutes, interlobular edema was observed at the termination of bypass. When bypass exceeded 100 minutes, the changes developed further and the animals died from pulmonary edema. Although new and improved equipment for extracorporeal circulation has prolonged the duration of safe total body perfusion in humans, post-perfusion pulmonary syndrome is still a serious problem in calves. Numerous explanations for these pulmonary complications have been advanced, including immaturity of the calf lung, excessive positive pressure ventilation[3, 49] improper positioning[66], and too rapid cessation of cardiopulmonary bypass.[5,69] Although we tried the measures suggested, no improvement was obtained. To see whether or not immaturity of the lung was important an animal weighing 110 kg was used for replacement with an artificial heart. The maximum pulmonary arterial pressures was 55 mm Hg shortly after pumping and remained higher than 30 mm Hg for approximately two hours. This shows that the species is more important than the maturity of the lung. Therefore, the reduction of cardiopulmonary bypass time to a minimum is one of the most important factors in reducing the post-perfusion pulmonary complication. Attention was focused on those steps of the anastomoses which were the most time consuming. As a result atrial cuffs with four tapes were used, and the artificial and natural aorta and pulmonary artery were anastomosed by tying the vessels over rigid teflon connectors. Particularly when a calf is used for the experiment, the shortness of the ascending aorta makes suture anastomosis difficult.

The time from commencement of pumping to closure of the chest was also important. In the spine position insufficient venous return to the right atrium occurs, even though the fluid balance was reasonable and the inferior vena cava was not obstructed. After the chest was closed and the animal was placed in the kneeling position, the mean systemic arterial pressure increased. Therefore, it is important that the animal with an artificial heart is placed in the kneeling position as soon as possible after pumping commences.

In early replacements excessive bleeding from the atrial anastomosis was a major postoperative problem. Leak-free anastomoses were difficult to achieve. Later, when the atrial cuffs separate from the ventricles were used, postoperative bleeding was markedly reduced, saving 30 minutes of operative time.

In most of the animals postoperative pulmonary hypertension was encountered. Pulmonary edema frequently occurred around the termination of cardiopulmonary bypass and developed further during the transition from cardiopulmonary bypass to the artificial heart. Even though the pump rate and pressure were gradually increased as cardiopulmonary bypass flow was reduced and residual fluid in the cardiopulmonary bypass circuit was gradually infused to maintain right atrial pressure within acceptable limits, postoperative pulmonary hypertension and edema occurred. Generally, pulmonary hypertension was treated first by making adjustments in the pump driving consoles to increase left ventricular output if possible, or by decreasing right ventricular output if possible and by frequently inflating the lungs with positive pressure between 30 and 35 mm H_2O. Continual pumping console adjustments were necessary

during the transition from cardiopulmonary bypass to the artificial heart. In order to reduce pulmonary edema to a minimum, an intravenous diuretic was given before termination of the cardiopulmonary bypass and after pumping with only the artificial heart[69]. Approximately one liter of urine output was obtained after two hours of pumping in cases where the systemic arterial pressure was maintained at the acceptable level.

In order to reduce postoperative pulmonary complication following cardiopulmonary bypass corticosteroid was given to the animals before and during bypass [22, 59]. The treated animals showed lower postoperative pulmonary arterial pressure and better arterial blood gas extensions than those of the untreated animals. Furthermore the systemic arterial pressure of the treated animals was maintained at a higher level than that of the untreated ones. In our experiments the pretreatment of animals with pharmacologic large doses of steroids before and during cardiopulmonary bypass decreased the pulmonary arterial resistance following bypass. Steroids given in large doses are said to act as vasodilators[51, 72]. Such a vasodilatating action could produce better peripheral tissue perfusion and diminish anaerobic metabolism and prevent metabolic acidosis[50, 71, 73]. When the pulmonary arterial pressure exceeds 40 mm Hg after pumping, it is necessary to reduce the right ventricular pump pressure. However, this causes the decrease in the left ventricular output, leading to metabolic acidosis. This acidosis then contributes to pulmonary arterial vasoconstriction[6,8,67]. Thus, a vicious circle arises.

C. Pulmonary Changes in the Subacute Phase

By the time the chest was closed and the animal was placed in

the kneeling position two hours of pumping had elapsed. Most of the animals were allowed to breathe spontaneously after four hours of pumping. The subacute phase is defined as the period from four hours to 48 hours after the start of pumping with the artificial heart.

The nine animals that died in the acute phase have already been discussed. This section describes and discusses the pulmonary function of the subacute phase and the postmortem pathological examinations of the lungs from 13 animals. These 13 animals died due to a variety of causes. The duration of pumping varied between six and 33 hours. If the 13 animals are grouped according to cause of death, then the pulmonary changes in the subacute phase are easy to understand. The animals that died due to any one cause had many points of similarity in their postoperative course. Two of 13 animals died accidently after eight hours of pumping; six animals died of low cardiac output after six to eight hours of pumping and five animals died of thromboembolism after 18 to 33 hours of pumping.

Lactic acid and pyruvic acid concentrations were determined in four animals which died of low cardiac output. The preoperative lactic acid concentrations were 9.5±4.5 mg% with pyruvic acid concentration of 0.41±0.09 mg%. In these four animals at the termination of the experiment, lactic acid concentration was between 140 and 354 mg% with pyruvic acid concentration of between 2.1 and 8.7 mg%. Base excess in six animals which died of low cardiac output reach -8 and -19 at the termination of the experiment. Cardiac output in three of these six animals was calculated by the dye dilution method and their cardiac outputs were only between 30 and 40 ml/kg/min after four hours of

pumping.

An increase in the pulmonary arterial pressure was present in five of the six animals around termination of the experiment. After approximately two hours of pumping the mean pulmonary arterial pressure of these animals decreased to less than 30 mm Hg and then was maintained at a level of between 10 and 25 mm Hg until approximately an hour prior to termination of the experiment. The mean value of the arterial pH of these five animals decreased gradually to 7.34 two hours prior to termination of the experiment. Then the pulmonary arterial pressure increased from 20 to 30 mm Hg during an hour prior to termination of the experiment and the arterial pH decreased from 7.29 to 7.19 (Fig. 34).

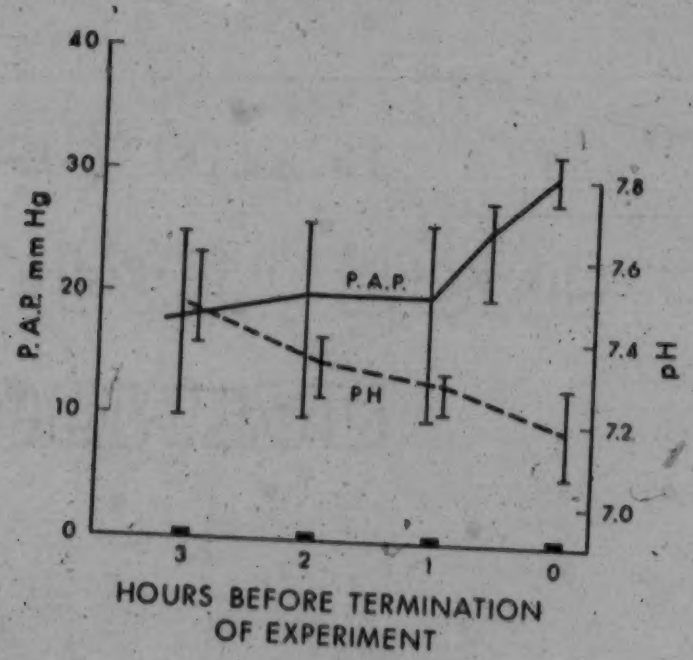

Fig. 34 The change in mean pulmonary arterial pressure and pH at termination of the experiment in animals that died due to low cardiac output.

One of the animals maintained the pulmonary arterial pressure at the level of between 20 and 18 mm Hg with the arterial pH of 7.52 ± 0.02 controlled by administration of sodium bicarbonate until termination of the experiment.

1. Death Due to Convulsion Caused by Thromboembolism

Among five animals that suffered death due to convulsion, one was mechanically assisted to breathe during the stable stage, which was approximately five hours after pumping to the occurrence of convulsion, and then was mechanically ventilated. Three others were allowed to breathe spontaneously during the stable stage with the supply of nasal oxygen and mechanically ventilated after occurrence of convulsion. The last one was allowed to breathe spontaneously with nasal oxygen from five hours after pumping to termination of the experiment.

These five animals attempted to stand up many times and passed a large amount of urine in the postoperative period.

During the stable stage the arterial pH was maintained at the level of 7.40 ± 0.02 without administration of sodium bicarbonate. The arterial oxygen saturation was at a reasonable level with the arterial pCO_2 of 40 ± 3 mm Hg. HCO_3^- concentration was 24 ± 2.5 milliequivalents with base excess of 0 ± 2. The mean systemic arterial pressure was maintained at the level of between 80 and 90 mm Hg. Cardiac output was calculated in three animals by the dye dilution method, and their cardiac output was 70 to 90 ml/kg/min at maximum. Lactic acid and pyruvic acid concentrations were 70 ± 2 mg% and 1.0 ± 0.1 mg% throughout

the experiment. These acid concentrations were markedly lower than those of the animals that suffered from death due to low cardiac output. None of the five animals were given sodium bicarbonate to control the arterial pH during the stable stage. The acid-base balance during the stable stage was normal. The first convulsions to attack the animals were of two types: one was a minor convulsion, which gradually changed into a more severe convulsion of greater frequency and duration; the other was a major convulsion, which killed the animal soon after. Four of the five animals were first attacked by minor convulsions after 12, 14, 24 and 27 hours of pumping respectively. One animal was attacked by a major convulsion after 32 hours of pumping.

Four animals which gradually suffered from progressive diastolic hypotension and died approximately between six and eight hours after the first convulsions. On the other hand, after a first major convulsion attack the tidal volume of the other animal decreased rapidly to between approximately 50 and 100 ml with difficulty in breathing. Thirty minutes after the first attack the animal expired.

The pulmonary arterial pressure was continuously monitored throughout the experiment in two of the animals. In the other three animals it was not monitored until termination of the experiment because the pulmonary pressure line was clotted or taken out in the stable stage. After approximately two hours of pumping the PAP was stable at the level of between 20 and 25 mm Hg. Then, once minor convulsion attacked the animals, the PAP increased gradually and the arterial pH decreased progressively. Three hours after the first attack of convulsions the PAP increased gradually and finally reached 44 mm Hg

with a decrease in the arterial pH of 7.20 (Fig. 35).

Figure 36 shows the blood pressures from one of the animals. After 24 hours of pumping the first short minor convulsion attacked the animal. The general condition of the animal and the blood gas examinations were still reasonable for the next two hours. However, as the minor convulsion changed into more severe convulsions of greater frequency and duration, the animal gradually developed systolic hypotension, accompanied with increases in the pulmonary arterial pressure and the left atrial pressure. Six hours after the first minor convulsions the animal developed widening of the systolic pressure and diastolic hypotension.

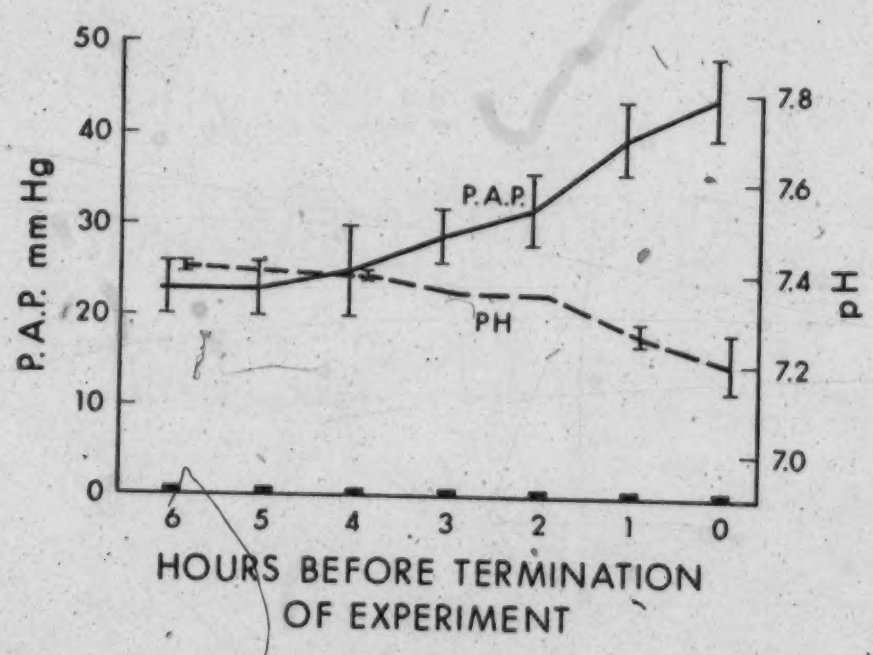

Fig. 35 The change in mean pulmonary arterial pressure and pH at termination of the experiment in animals that died due to convulsions.

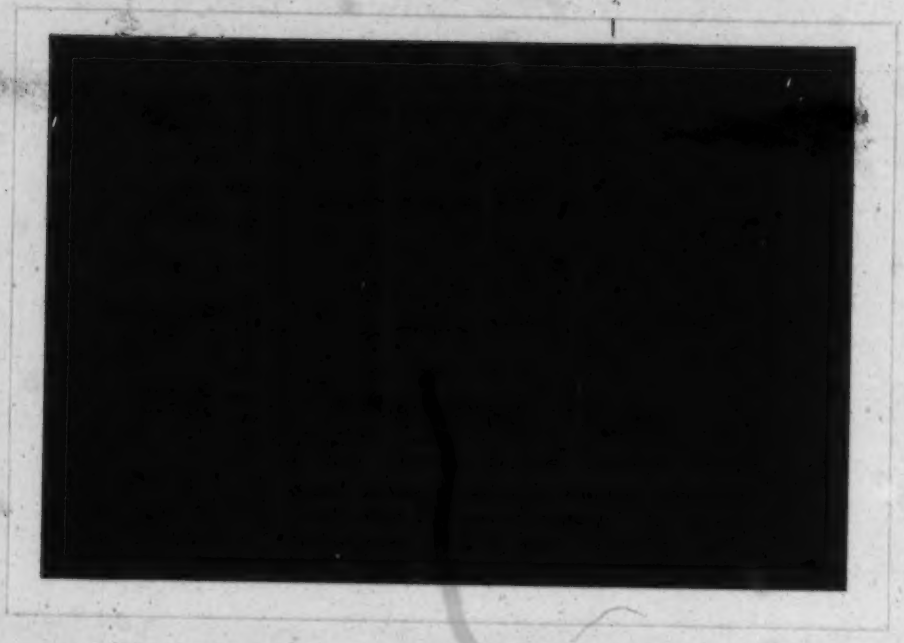

Fig. 36 Blood pressures from an animal that had the first minor convulsion after 24 hours of pumping.

2. Postmortem Pathological Examination of the Lungs

The lungs from 13 animals that died due to various causes in the subacute phase were examined macroscopically and microscopically. In all animals acute passive congestion was observed in the dorsal parts of the lower lobes of the lungs during and after cardiopulmonary bypass. In some animals the interlobular edema was seen slightly in the dorsal parts of the lower lobes at termination of bypass. However, as soon as pulmonary circulation was recommenced by pumping with an artificial heart, acute passive congestion in the dorsal parts of the lower lobes disappeared quickly and interlobular edema disappeared gradually. As the chest was closed, the lungs appeared normal.

In two animals that suffered from accidental death, the lungs were deteriorated to a minor degree of severity. Most parts of the upper and middle lobes preserved good aeration and normal alveolar architecture. Thirty percent of each lung, mainly dorsal parts of the lower lobes, was atelectatic and slightly congested. On a section of congested area in the lower lobes frothy fluid was observed sparsely in the respiratory tract. No pieces of lung taken from multiple sites sank to the bottom (Table 12).

In the animals that died due to low cardiac output the lungs deteriorated to a moderate degree of severity (Table 12).

The lower lobes of the lungs were moderately edematous and congested. Also, atelectasis and hemorrhage were seen occasionally throughout the lungs. On a section of the lobes that were congested and edematous, a moderate amount of frothy fluid was observed in the respiratory tract. Pieces of lung taken from the congested lobes sank to the bottom.

TABLE 12

PATHOLOGICAL FINDINGS IN THE LUNGS FROM ANIMALS THAT DIED AFTER 4 HOURS OF PUMPING

Cause of Death	Heart Type	Duration of Pumping (hrs. min)	Pathohistological Findings
Mechanical Failure	Sac	8:10	30% atelectasis in dorsal parts of lower lobes.
	MK XII	to 8:20	Slight congestion, edema and hemorrhage in dorsal parts of lower lobes.
Low Cardiac Output	Sac MK IX and MK XII	6:50 to 10:05	80% atelectasis. Moderate congestion, edema and hemorrhage throughout the lungs. Perivascular hemorrhage in the lungs with a MK IX heart.
Convulsion	Sac	18:25 to 33:15	80% atelectasis. Severe congestion and hemorrhage, and moderate edema throughout the lungs. Fibrin platelet thrombi in the animals surviving more than 30 hours.
	MK XII	32:50	Moderate congestion, hemorrhage and slight edema in the lower lobes.

Intra-alveolar edema and hemorrhage were seen, often accompanied by interlobular edema and hemorrhage. Perivascular hemorrhage was seen around the small pulmonary arteries in those cases in which a MK IX artificial heart was used (Fig. 37).

Fig. 37 The lung from an animal with a MK IX artificial heart after 8 hours of pumping. Note the perivascular hemorrhage and intra-alveolar edema. (H.E. x50)

In the lungs from animals that suffered from convulsion, the severity of deterioration varied markedly (Table 12). Approximately 80% of the lungs was atelectatic, edematous and congested. Much frothy fluid flowed from sections of the lungs. Most pieces of lung taken from multiple sites sank to the bottom. Severe intra-alveolar hemorrhage and edema were seen under the microscope. Some bronchioli were occluded by a large number of red blood cells and the Eosin stained material and

thromboemboli were found in the pulmonary vessels.

Two animals that survived 33 and 31 hours showed excessive hemorrhage, atelectasis congestion and edema (Fig. 38). None of the lobes was normal. Normal regions, appearing like an island, were occasionally observed. An examination of the pulmonary arteries revealed several thromboemboli riding on the bifurcation of the arteries and "fibrin platelet thrombi" were occasionally seen in the pulmonary vessels (Fig. 39). Intra-alveolar edema, hemorrhage and congestion were also seen.

Fig. 38 The lungs from an animal with a sac-type artificial heart after 31 hours of pumping. Note the marked congestion, atelectasis, hemorrhage and edema.

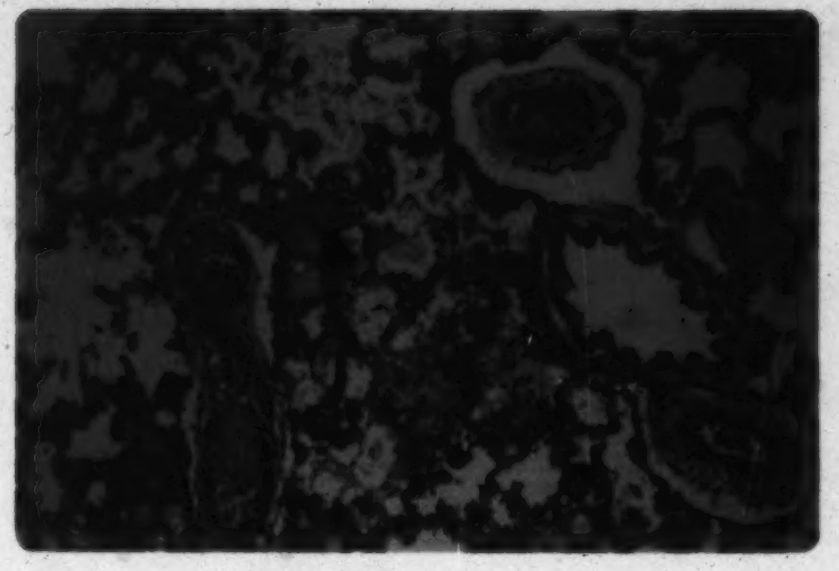

Fig. 39 The lung from an animal after 33 hours of artificial heart pumping. Note the congestion, intra-alveolar edema, and fibrin platelet thrombi in the vessels. (H.E. x 100)

In the animal that died soon after the first major convulsion approximately 40% of lower lobe tissue of the lungs was congested and hemorrhagic. Approximately 20% of the middle and upper lobe tissue was edematous (Fig. 40). A section of the pulmonary arteries revealed a fibrous fibrin embolus at the junction between a large pulmonary artery and a small pulmonary artery (Fig. 41). Sparse frothy fluid was observed only in edematous and congested regions. Moderate interlobular edema and subpleural hemorrhage were seen in the congested regions. Some small bronchioli contained monostructural Eosin stained material. Most parts of the lungs preserved good aeration and good alveolar architecture.

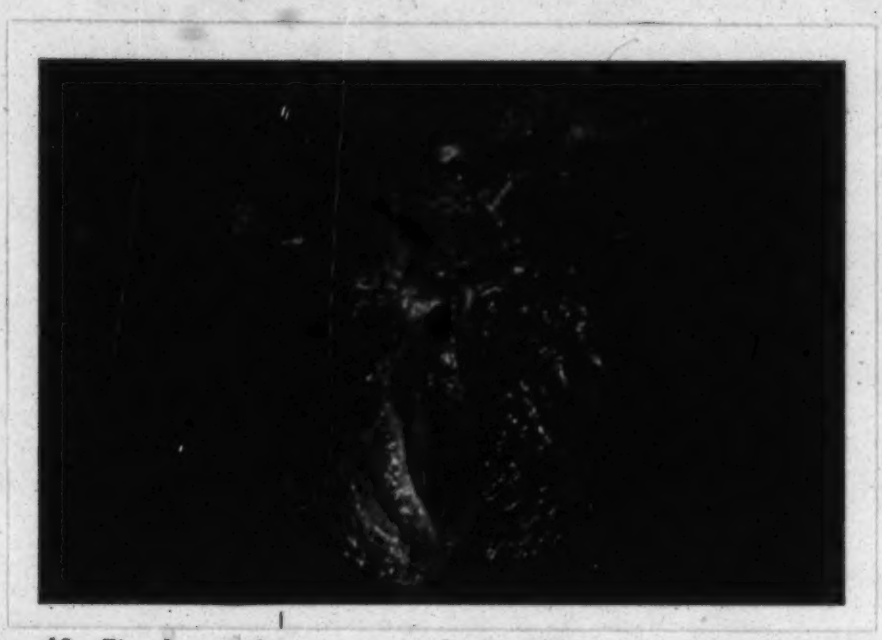

Fig. 40 The lungs from an animal that died soon after the first major convulsion (sacrificed after 33 hours of artificial heart pumping). Note the moderate congestion in the lower lobes.

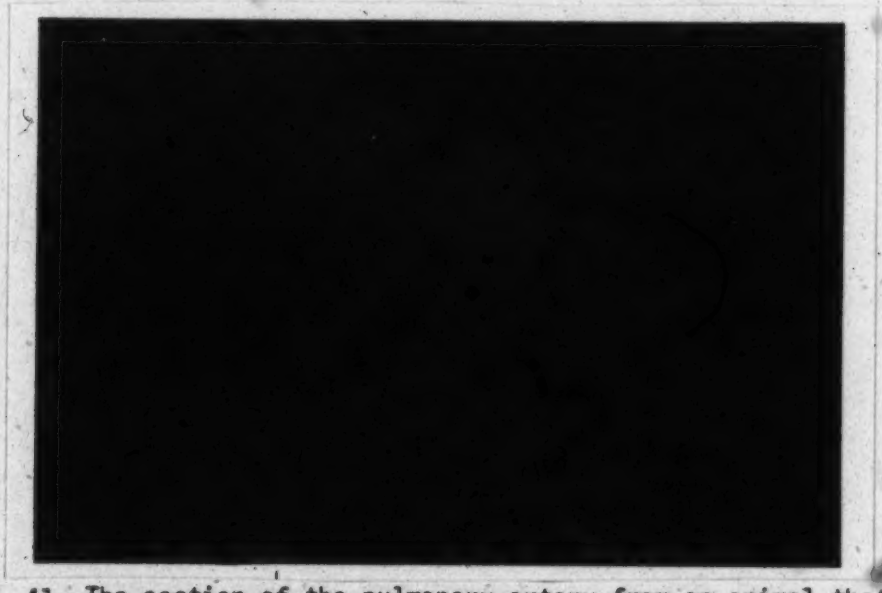

Fig. 41 The section of the pulmonary artery from an animal that had the first major convulsion after 33 hours of a MK XII artificial heart pumping. Note a fibrous fibrin embolus at the junction between a large pulmonary artery and a small pulmonary artery. The same material was found in the vicinity of valves and at the junction between the diaphragm and the housing of an artificial heart.

Deterioration of the lungs can be summarized as follows:

(1) In the subacute phase there was no difference of functional and morphological changes in the lungs between the animals pretreated with Methylprednisolone and the untreated animals.

(2) Severity of deterioration of the lungs was related to the severity of acidosis and its duration.

(3) The animals that recovered very well after pumping and that suddenly suffered death from accident or major convulsions developed a minor degree of pulmonary deterioration.

(4) The animals that recovered very well after pumping and then gradually suffered from metabolic acidosis after attacks of minor convulsions, developed a major degree of pulmonary deterioration.

(5) Perivascular hemorrhage around the small pulmonary arteries was seen in the lungs from the animals that had a diaphragm-type MK IX artificial heart.

DISCUSSION

Low cardiac output and thromboembolism are two major factors contributing to the prognosis of the animals with total artificial heart replacement.[3,46,63,64] After the animals suffer from low cardiac output and/or convulsion caused by thromboemboli. Low cardiac output in the subacute phase is primarily caused by compression of the venous system by the artificial heart. If the artificial heart is larger than its physiological space, i.e., the pericardium, relatively rigid chambers will compress the surrounding soft veins. If the heart

has too large an antero-posterior diameter, the chest wall will compress the inferior vena cava and pulmonary veins by pushing the heart against them. If the width of the heart is too great, it will compress the pulmonary venous system and the inferior vena cava. When the diaphragm-type MK IX artificial heart was used, the inferior vena cava was always compressed by the heart after the chest was closed. In order to avoid this complication a larger experimental animal weighing 110 kg was used but the animal suffered from compression of the inferior vena cava.

The second mechanical problem is the weight of the artificial heart, particularly the ventricle. If the artificial heart is excessively heavy, the intrathoracic venous system will be compressed in the supine position and stretched in the kneeling position. The inferior vena cava is easily affected by these problems because it is separate from the chest wall and positioned at the middle of the depth of the thorax.

The angle of anastomosis between the natural right atrium and the artificial atrium (graft or cuff) is important in order to obtain good venous return from the inferior vena cava. Even though the proper angle was kept before closure of the chest, the angle changed inside the chest after closure. Usually this did not produce any kinking of the artificial atrium; however, on rare occasions the rim of the right atrial cuff pushed the natural atrial wall against the chest wall and occluded the orifice of the inferior vena cava.

The diaphragm-type MK XII artificial heart which was smaller by 25% than the MK IX heart partially resolved these problems.

Thromboembolism is a serious problem in the animals that survive for more than 24 hours[46]. There are two places which produce thrombi

in the subacute phase: one is inside the artificial heart and the other is inside the monitoring pressure lines. Since the thrombus formation inside the artificial heart has been described and discussed in the previous section it is omitted here.

Thrombus formation inside the monitoring pressure lines is not a problem to be overlooked. Heparin was neutralized by Protamine-sulphate after pumping and the whole blood clotting time was controlled to between 8 and 12 minutes throughout the experiment, if possible. In most animals that survived for more than eight hours the monitoring pressure lines were so often clotted that they had to be flushed out. In the series of bypass control one of the animals suffered death from convulsions after 24 hours of bypass. The systemic arterial pressure line was often flushed out before the animal suffered from convulsions. At autopsy a thromboembolus was observed in the left thalamus of the brain. Focal infarcts were occasionally found in the kidneys and thromboemboli were seen in the renal arteries. No thrombus was found inside the heart. Therefore, in the later experiments the pulmonary arterial, the right atrial and left atrial pressure lines were pulled out just before closure of the chest. The systemic arterial and the central venous lines were left for the arterial blood examinations and infusion of fluids.

Once the animal suffered from either low cardiac output due to compression of the inferior vena cava by the artificial heart or convulsions caused by thromboembolism, the pulmonary function gradually deteriorated, and there was marked edematous congestion in the lungs. Metabolic acidosis due to low cardiac output[18,34,68] increases

the adrenal secretion[21,32]. Also, aerobic oxidation of carbohydrate (tricarboxylic acid cycle) is reduced and is accompanied by an accumulation of pyruvic acid and lactic acid[12]. These agents contribute to the pulmonary deterioration. Simultaneously, sodium is accumulated in the body because urine output decreases due to low renal perfusion and also because sodium bicarbonate is given intermittently in order to maintain an acceptable pH. Pulmonary edema is also associated with this sodium retention[27].

After the animal suffers from convulsions, alterations in the acid-base balance occur due to metabolic acidosis.[9,34] Thrombo-embolism contributes to the production of serotonin and cathecholamines, and to the liberation of histamine. These agents contribute to an increasing pulmonary capillary pressure and cause an increase in permeability.[10,16,28,35,86,87]

Perivascular hemorrhage strongly suggests tissue hypoxia.[19,80] It was only seen in the lungs and brains from animals with diaphragm-type MK IX artificial heart implants. Even though the animals that had either a sac-type artificial heart or diaphragm-type MK XII artificial heart suffered from severe metabolic acidosis, perivascular hemorrhage was not seen in any organs. It seems that another factor contributes to the occurrence of perivascular hemorrhage. The pressure wave pattern of a diaphragm-type MK IX artificial heart shows a sharp systolic dp/dt with a rapid diastolic descent (Fig.8). The pressure wave pattern of either a sac-type artificial heart or a diaphragm-type MK XII artificial heart shows a moderate systolic dp/dt with a slow diastolic descent (Fig. 4, 9). When the small peripheral arteries become frail due to severe metabolic

acidosis[15,29,30] they cannot withstand the sharp arterial pressure wave pattern, and leak both plasma and erythrocytes.

CHAPTER IV

SUMMARY AND CONCLUSIONS

From November 1971 to November 1972 the natural heart in 22 calves weighing between 65 and 90 kg was replaced with a total artificial heart. During the replacement cardiopulmonary bypass was used to support the animal. Nine of these artificial hearts were sac-type and 13 were diaphragm-type design.

Of the 22 animals receiving an artificial heart, six had good postoperative recovery. They all passed a large amount of urine, responded to sight and sound and attempted to stand up several times. Three of these six animals survived more than 30 hours with an artificial heart. The maximum survival time was 33 hours.

Seven of the 22 animals died within eight hours of pumping as a result of low cardiac output, primarily due to compression of the inferior vena cava by the artificial heart. Five animals died due to convulsion caused by thromboembolism after 18 to 33 hours of pumping. Four others died from severe acute pulmonary complication within four hours after pumping commenced and six died due to miscellaneous causes (two mechanical failures, two surgical failures and two accidents).

Of the nine animals with a sac-type artificial heart, four died due to convulsion, and two due to severe acute pulmonary complication. Three animals died of other causes (one accident, one mechanical failure and one low cardiac output). Of the 13 animals with a diaphragm-type artificial heart, six died due to low cardiac output and two due to

severe acute pulmonary complication. Five animals died from other causes (two surgical failures, one mechanical failure, one accident and one convulsion). Therefore, low cardiac output, thromboembolism and acute pulmonary complication were the three common causes of death.

Most of the animals showed mean pulmonary arterial pressures (PAP) between 40 and 65 mm Hg which reached a maximum after five minutes of pumping with the artificial heart. Of the three animals with maximum PAP higher than 70 mm Hg, two were sacrificed due to severe acute pulmonary complication. Both animals that underwent total cardio-pulmonary bypass for about two hours were sacrificed due to severe acute pulmonary edema after two hours of pumping with an artificial heart. There was no correlation between the postoperative maximum PAP and the type of artificial heart used. However, the five animals pretreated with Methylprednisolone showed a postoperative maximum PAP less than 50 mm Hg which was much lower than that of the untreated animals.

In half of the animals with an artificial heart, the PAP decreased gradually to less than 30 mm Hg within an hour after pumping began. Two animals maintained PAP higher than 30 mm Hg for a two hour postoperative period and two for more than four hours of pumping. In five animals treated with Methylprednisolone the PAP decreased rapidly to 28 mm Hg after 30 minutes of pumping.

The mean systemic arterial pressure (SAP) reached 60 mm Hg after ten minutes of pumping, and was maintained between 60 and 70 mm Hg until the animal's chest was closed. In the animals with a sac-type artificial heart the SAP increased further to between 70 and 90 mm Hg after the chest was closed and the animals were placed in the kneeling

position. However, in most of the animals with a diaphragm-type artificial heart the SAP decreased to between 40 and 50 mm Hg after the chest was closed because the artificial heart compressed the inferior vena cava.

The mean arterial oxygen saturation was approximately 70% with a pCO_2 of 30 to 40 mm Hg immediately after pumping commenced. After approximately one and a half hours of pumping the arterial oxygen saturation of the animals with a sac-type artificial heart increased to 95% with a decrease in pCO_2, while that of the animals with a diaphragm-type artificial heart was approximately 80% with an increase in pCO_2. In the animals treated with Methylprednisolone the arterial oxygen saturation was 90% immediately after pumping commenced and after one and a half hours of pumping it was 98% with a respiratory alkalosis.

In all animals acute passive congestion was observed in the dorsal parts of the lower lobes of the lungs during and after cardiopulmonary bypass. In most of the animals that underwent cardiopulmonary bypass for more than 80 minutes the interlobular edema was observed in the dorsal parts of the lower lobes around termination of bypass. As soon as the pulmonary circulation was recommenced by pumping with the artificial heart, the acute passive congestion disappeared quickly, and the interlobular edema faded slowly. However, if the PAP increased to higher than 70 mm Hg, the lungs became congested and finally copious amounts of frothy, hemorrhagic fluid were expelled through the endotracheal tube. At postmortem examination the lungs showed dominant congestion. In the animals that underwent cardiopulmonary bypass for

approximately two hours, there was a marked development of interlobular edema as the pumping time increased. The animals expelled frothy fluid through the endotracheal tube. At autopsy the lungs showed dominant edema.

Of the nine animals that died in the acute phase, four suffered from severe acute pulmonary complication, two from surgical failure, and three from mechanical failure, accident, and low cardiac output respectively.

Of the 13 animals that died in the subacute phase, one died from mechanical failure, one from an accident after eight hours of pumping, six from low cardiac output with six to eight hours of pumping, and five from convulsions after 18 to 33 hours of pumping.

The two animals that suffered either mechanical failure or accident maintained a reasonable level of arterial oxygen saturation, a mean pH 7.40, pCO_2 32 ± 2 and base excess -3 milliequivalents per liter until termination of the experiments. At postmortem examination the dorsal parts of the lower lobes of the lungs were slightly congested and edematous.

Of the six animals that suffered from low cardiac output, a severe metabolic acidosis was present in four with mean pH 7.28, pCO_2 30 mm Hg, and base excess -12 milliequivalents per liter. Approximately an hour before termination of the experiment one other animal developed combined metabolic and respiratory acidosis. The last animal showed respiratory alkalosis with renal compensation. An increase in the PAP was present in five animals around termination of the experiment, as the arterial pH decreased. At autopsy approximately 80% of each

lung showed atelectasis. Moderate congestion, edema and hemorrhage were seen throughout the lungs and perivascular hemorrhage was found in the lungs from the animals with a diaphragm-type MK IX artificial heart.

All five animals that died of convulsions maintained reasonable levels of pH, pO_2 and pCO_2 during the stable stage. This lasted from approximately five hours after pumping commenced until the occurrence of convulsion. The acid-base balance during the stable stage was normal (pH 7.40 ± 0.02, pCO_2 40 ± 3 mm Hg, and base excess 0 ± 2). Four of five animals first had a minor convulsion after 12, 14, 24 or 27 hours of pumping. As these minor convulsions gradually changed into more severe convulsions of greater frequency and duration, two animals developed respiratory acidosis; the other two developed metabolic acidosis. The PAP increased gradually after approximately two hours of convulsions and finally reached 45 mm Hg. Simultaneously, the arterial pH decreased from 7.40 to 7.20 during the last four hours of pumping. At postmortem examination 80% of each lung showed atelectasis. Severe congestion, hemorrhage, and moderate edema were seen throughout the lungs. On the other hand, the last animal had major convulsions without warning and expired 30 minutes later. At autopsy moderate congestion, hemorrhage and slight edema were seen in the lower parts of lower lobes of the lungs.

1. AFFELD, K., BUCHERL, E.S., MOHNHAUPT, R., KRAUTZBERGER, W., KEILBACH, H., KLEINE, H., WALLNER, F. and CLEVERT, D.: An artificial heart implanted in the abdominal wall. Trans. Amer. Soc. Artif. Int. Organs 17: 464-467, 1971.

2. AKUTSU, T. and KOLFF, W.J.: Permanent substitute for valves and hearts. Trans. Amer. Soc. Artif. Int. Organs 4: 230-232, 1958.

3. AKUTSU, T., MIRKOVITCH, V., TOPAZ, S.R. and KOLFF, W.J.: Silastic sac-type of artificial heart and its use in calves. Trans. Amer. Soc. Artif. Int. Organs 9: 281-285, 1963.

4. AKUTSU, T., TAKAGI, H. and TAKANO, H.: Total artificial hearts with built-in valves. Trans. Amer. Soc. Artif. Int. Organs 16: 392-397, 1970.

5. AKUTSU, T., TOPAZ, S.R., MIRKOVITCH, V., PANAYOTOPOULOS, E. and KOLFF, W.J.: Problems in calf lungs immediately after implantation of an artificial heart. Trans. Amer. Soc. Artif. Int. Organs 10: 162-165, 1964.

6. ALMOND, C.H., JONES, J.C., SNYDER, H.M., MEYER, B.W. and PATRICK, J.: Hypoxia of the lung parenchyma during cardiopulmonary bypass. Arch. Surg. 93: 986-989, 1966.

7. ATSUMI, K., HORI, M., IKEDA, S., SAKURAI, Y., FUJIMORI, Y. and KIMOTO, S.: Artificial heart incorporated in the chest. Trans. Amer. Soc. Artif. Int. Organs 9: 292-298, 1963.

8. BALIS, J.U., COX, W.D., PIFARRE, R. and NEVILLE, W.E.: The role of pulmonary hypoxia in the post perfusion lung syndrome. Surg. Forum 20: 205-207, 1969.

9. BANE, A.E., TRAGUS, E.T. and PARKINS, W.M.: Effects of sodium chloride and bicarbonate in shock with metabolic acidosis. Amer. J. Physiol. 212: 54-60, 1967.

10. BECK, L.: Histamine as the potential mediator of active reflex dilatation. Fed. Proc. 24: 1298-1310, 1965.

11. BENNETT, C.R., SMOOKLER, H.H. and BUCKLEY, J.P.: Prevention of ventricular fibrillation during induced hypothermia by P-286. J. Pharmacol. Exp. Ther. 159: 115-122, 1968.

12. BERTRAM, F.K., WASSERMAN, K. and VAN KESSEL, A.L.: Gas exchange following lactate and pyruvate injections. J. Appl. Physiol. 23: 190-194, 1967.

13. BONCHEK, L.I., TATOOLES, C.J. and BRAUNWALD, N.S.: Experimental cardiac surgery in the calf. Techniques of anesthesia and operation. Ann. Thor. Surg. 3: 211-217, 1967.

14. BOYETT, J.D., STOWE, D.E., BECKER, L.H. and BRITZ, W.E.: Rapid method for determination of cardiac output by indicator dilution techniques. J. Lab. Clin. Med. 64: 160-167, 1964.

15. BRIGGS, J.N. and HOGG, G.: Perinatal pulmonary pathology. Pedia. 22: 41-48, 1958.

16. BRODY, M.J.: Neurohumoral mediation of active reflex vasodilatation. Fed. Proc. 25: 1583-1592, 1966.

17. BURNS, W.H., SHUMACKER, H.B. and LOUBIER, R.J.: The totally implantable mechanical heart: an appraisal of feasibility. Ann. Surg. 164: 445-456, 1966.

18. CANNON, W.B.: Acidosis in cases of shock, hemorrhage and gas infection. J. Amer. Med. Ass. 70: 531-535, 1918.

19. CLIFFORD, S.H.: The effects of asphyxia on the newborn infant. J. Pediat. 18: 567-578, 1941.

20. COOLEY, D.A. et al.: Staged replacement of the human heart. Trans. Amer. Soc. Artif. Int. Organs 15: 252-263, 1969.

21. DARBY, T.O. and WATTS, D.T.: Acidosis and blood epinephrine levels in hemorrhagic hypotension. Amer. J. Physiol. 206: 1281-1284, 1964.

22. DAVIES, A.L., JUCA, E.R. and AUSTEN, W.G.: Left ventricular function in steroid pretreated dogs following cardiopulmonary bypass. J. Cardiovasc. Surg. (Torino) 9: 273-277, 1968.

23. DAW, E.F., MOFFITT, E.A., MICHENFELDER, J.D. and TERRY, H.R.: Profound hypothermia. Canad. Anaes. Soc. J. 11: 382-393, 1964.

24. DE VRIES, W.C., KWAN-GETT, C.S. and KOLFF, W.J.: Consumptive coagulopathy, shock and the artificial heart. Trans. Amer. Soc. Artif. Int. Organs 16: 29-36, 1970.

25. DONAWICK, W.J., NARA, Y. and BANE, A.E.: Techniques for successful cardiopulmonary bypass in the calf. J. Surg. Res. 9: 79-85, 1969.

26. GAUERT, W.B., ANDERSON, D.S., REED, W.A. and TEMPLETON, A.W.: Pulmonary complications following extracorporeal circulation. South Med. J. 64: 679-686, 1971.

27. GETT, P.M., JONES, E.S. and SHEPHERD, G.F.: Pulmonary edema associated with sodium retention during ventilator treatment. Br. J. Anesth. 43: 460-470, 1971.

28. GUREWICH, V., COHEN, M.L. and THOMAS, D.P.: Humoral factors in massive pulmonary embolism: an experimental study. Amer. Heart J. 76: 784-794, 1968.

29. HART, E.W.: Hemorrhagic states in the newborn. Practitioner 197: 330-337, 1966.

30. HERAUX, A.: Les hemorragies du prématuré. Etude anatomo-pathologique. Sem. Hos. Paris 25: 3765-3771, 1949.

31. HERSHGOLD, E.J., KWAN-GETT, C.S., KAWAI, J. and ROWLEY, K.: Hemostasis coagulation and the total artificial heart. Trans. Amer. Soc. Artif. Int. Organs 18: 181-185, 1972.

32. HIGASHI, R.: Effect of metabolic acidosis on adrenaline and noradrenaline secretion of the innervated and denervated adrenal gland in the dog. Tohoku. J. Exp. Med. 89: 77-84, 1966.

33. HOUSTON, S., AKUTSU, T. and KOLFF, W.J.: Pendulum type of artificial heart within the chest: Preliminary report. Amer. Heart J. 59: 723-730, 1960.

34. HUCKABEE, W.E.: Relationships of pyruvate and lactate during anaerobic metabolism - effects of infusion of pyruvate or glucose and of hyperventilation. J. Clin. Invest. 37: 244-254, 1958.

35. KABINS, S.A., MOLINA, C. and KATZ, L.N.: Pulmonary vascular effects of serotonin (5-OH-tryptamine) in dogs: its role in causing pulmonary edema. Amer. J. Physiol. 197: 955-958, 1959.

36. KIMOTO, S., ATSUMI, K., SAKURAI, Y. et al.: Studies on the artificial heart driven with controlled gas pressure device on the pressure generator for universal use. Trans. Amer. Soc. Artif. Int. Organs 10: 66-68, 1964.

37. KINGSLEY, G.R. and ROBNETT, B.A.: New dye method for direct photometric determination of calcium. Amer. J. Clin. Path. 27: 223-230, 1957.

38. KLAIN, M., MRAVA, G.L., TAJIMA, K., SCHRIBER, K., WEBB, J., OGAWA, H., OPPLT, J. and NOSE, Y.: Can we achieve over 100 hours survival with a total mechanical heart? Trans. Amer. Soc. Artif. Int. Organs 17: 437-444, 1971.

39. KNIGHT, C.J., JULIAN, D.G., MACLEOD, N., TAYLOR, D.E.M. and WADE, D. An artificial heart with independently variable pulse parameters. Trans. Amer. Soc. Artif. Int. Organs 17: 433-436, 1971.

40. KOHNO, R., MIURA, I., TSUCHIYA, K., MATSUDA, Y. and MIURA, S.: Prevention of coagulation by the ultrasonic. Jap. J. Thorac. Surg. 24: 355-358, 1971.

41. KOLFF, W.J.: An artificial heart inside the body. Scientific Amer. 213: 38-46, 1965.

42. KOLFF, W.J., AKUTSU, T., DREYER, B. and NORTON, H.: Artificial heart in the chest and use of polyurethane for making hearts, valves and aorta. Trans. Amer. Soc. Artif. Int. Organs 5: 298-303, 1959.

43. KUSSEROW, B.K.: A permanently indwelling intracorporeal blood pump to substitute for cardiac function. Trans. Amer. Soc. Artif. Int. Organs 4: 227-230, 1958.

44. KWAN-GETT, C.S., BACKMAN, D.K., DONOVAN, F.M., EASTWOOD, J.N., FOOTE, J.L., KAWAI, J., KESSLER, T.R., KRALIOS, A.C., PETERS, J.L., VAN KAMPEN, K.R., WONG, H.K., ZWART, H.J. and KOLFF, W.J.: Artificial heart with hemispherical ventricles II and disseminated intravascular coagulation. Trans. Amer. Soc. Artif. Int. Organs 17: 474-481, 1971.

45. KWAN-GETT, C.S., COLLAN, Y.W., JACOBSEN, S. and KOLFF, W.J.: Total replacement artificial heart and driving system with inherent regulation of cardiac output. Trans. Amer. Soc. Artif. Int. Organs 15: 245-251, 1969.

46. KWAN-GETT, C.S., VAN KAMPEN, K.R., KAWAI, J., EASTWOOD, N. and KOLFF, W.J.: Results of total artificial heart implantation in calves. J. Thorac. Card. Surg. 62: 880-889, 1971.

47. KWAN-GETT, C.S., ZWART, H.J., KRALIOS, A.C., KESSLER, T., BACKMAN, K. and KOLFF, W.J.: A prosthetic heart with hemispherical ventricles designed for low hemolytic action. Trans. Amer. Soc. Artif. Int. Organs 16: 409-415, 1970.

48. LARSON, R.E. and McGOON, D.C.: Experimental cardiac surgery in calves. II. Management for aortic valve surgery. J. Surg. Res. 3: 104-111, 1963.

49. LARSON, R.E., MOFFITT, E.A. and McGOON, D.C.: Experimental cardiac surgery in calves. I. Anesthesia. J. Surg. Res. 3: 101-103, 1963.

50. LILLIHEI, R.C., LONGERBEAN, J.K., BLOCK, J.H. and MANNAX, W.G.: The nature of irreversible shock: Experimental and clinical observation. Ann. Surg. 160: 682-710, 1964.

51. LILLEHEI, R.C., LONGERBEAM, J.K., BLOCK, J.H. and MANAX, W.G.: The modern treatment of shock based on physiologic principles. Clin. Pharmacol. Therap. 5: 63-101, 1964.

52. LIOTTA, D., TALIANI, T. and GIFFONIELLA, A.H.: Artificial heart in the chest: Preliminary report. Trans. Amer. Soc. Artif. Int. Organs 7: 318-323, 1961.

53. LYMAN, D.J., BRASH, J.L. and KLEIN, K.G.: The effect of chemical structure and surface properties of synthetic polymers on the coagulation of blood. Proc. Artif. Heart Program Conf. 113, June 9-13, 1969.

54. McCABE, S.P.: Pump for replacement of the heart. Trans. Amer. Soc. Artif. Int. Organs 5: 289-292, 1959.

55. MOHRI, H., DILLARD, D.H., CRAWFORD, W.E., MARTIN, W.E. and MERENDINO, K.A.: Method of surface-induced deep hypothermia for open-heart surgery in infants. J. Thorac. Cardiovasc. Surg. 58: 262-270, 1969.

56. MOHRI, H., HESSEL, E.A., NELSON, R.J., MATANO, I., ANDERSON, H.N., DILLARD, D.H. and MERENDINO, K.A.: Use of Rheomacrodex and hyperventilation in prolonged circulatory arrest under deep hypothermia induced by surface cooling. Method for open heart surgery in infants. Amer. J. Surg. 112: 241-250, 1966.

57. MORRIS, D.T. and COUVES, C.M.: Experiences with a sac-type artificial heart. C.M.A.J. 105: 483-487, 1971.

58. MORRIS, D.T., NISHIZAWA, T. and COUVES, C.M.: Design and performance characteristics of an artificial heart. Jap. J. Thorac. Surg. 26: 191-194, 1973.

59. MOSES, M.L., CANISHION, R.C., TOKUNAGA, K., PIERUCCI, L., DAVIES, A.L. and NEALON, T.F.: Effect of corticosteroid on the acidosis of prolonged cardiopulmonary bypass. J. Surg. Res. 6: 354-360, 1966.

60. MOTT, W.E. and COLE, D.W.: Development of a nuclear powered artificial heart. Trans. Amer. Soc. Artif. Int. Organs 18: 152-157, 1972.

61. NISHIZAWA, T., MORRIS, D.T. and COUVES, C.M.: Result of total artificial heart implantation in calves. Jap. J. Thorac. Surg. 26: 271-275, 1973.

62. NISHIZAWA, T., MORRIS, D.T. and COUVES, C.M.: Results of total artificial heart replacement: causes of death and histological examination. Iryo (Therapy in Japan), in press, 1973.

63. NOSE, Y. and KOLFF, W.J.: Some experiences with artificial hearts inside the chest, driven with a simple inexpensive servo-system. J. Cardiovasc. Surg. 9: 22-30, 1968.

64. NOSE, Y., SARIN, C.L., KLAIN, M., LEITZ, K.H., TESNY, T.J., PHILLIPS, P.M., ROSE, F.L. and KOLFF, W.J.: Elimination of some problems encountered in total replacement of the heart with an intrathoracic mechanical pump: venous return. Trans. Amer. Soc. Artif. Int. Organs 12: 301-309, 1966.

65. NOSE, Y., YAJIMA, K., IMAI, Y., KLAIN, M., MRAVA, G., SCHRIBER, K., URBANEK, K. and OGAWA, H.: Artificial heart constructed with biological material. Trans. Amer. Soc. Artif. Int. Organs 17: 482-487, 1971.

66. NOSE, Y., TOPAZ, S., SEN GUPTA, A., TRETBAR, L.L. and KOLFF, W.J.: Artificial hearts inside the pericardial sac in calves. Trans. Amer. Soc. Artif. Int. Organs 11: 255-262, 1965.

67. PANETH, J., SELLERS, R., GOTT, V.L., WEINICH, W.L., ALLEN, P., READ, R.C. and LILLEHEI, C.W.: Physiologic studies upon prolonged cardiopulmonary bypass with the pump-oxygenator with particular reference (1) Acid-base balance, (2) Siphon caval drainage. J. Thorac. Surg. 34: 570-579, 1957.

68. ROBINSON, J.S.: Acidosis in low flow states. Int. Anesthesiol. Clin. 7: 895-903, 1969.

69. ROSS, J.N., AKERS, W.W., O'BANNON, W., SPARGO, W.J., SERRATO, M.A., FUQUA, J.M., RUARK, B.S., WIETING, D.W., KENNEDY, J.H. and DE BAKEY, M.E.: Problems encountered with development and implantation of the Baylor-Rice orthotopic cardiac prosthesis. Trans. Amer. Soc. Artif. Int. Organs 18: 168-175, 1972.

70. SALISBURY, P.F.: Implantation of physiological machines into the mammalian organism. Identification of problems connected with the implantation of artificial hearts and of artificial kidneys. Experimental results to date. Trans. Amer. Soc. Artif. Int. Organs 3: 37-42, 1957.

71. SAMBHI, M.P., WEIL, M.H. and UDHOJI, V.N.: Acute pharmacodynamic effects of glucocorticoids: Cardiac output and related hemodynamic changes in normal subjects and patients in shock. Circulation 31: 523-530, 1965.

72. SAMBHI, M.P., WEIL, M.H., UNDOJI, V.N. and SHUBIN, M.: Adrenocorticoids in the management of shock. Internat. Anesth. Clin. 2: 421-433, 1964.

73. SCHUMER, W. and NYHUS, L.M.: Corticosteroids in the treatment of shock: Symposium conducted by the University of Illinois College of Medicine, Department of Surgery, April 13, 1968. Chicago.

74. SEIDEL, W., AKUTSU, T., MIRKOVITCH, V., BROWN, D. and KOLFF, W.J.: Air-driven artificial hearts inside the chest. Trans. Amer. Soc. Artif. Int. Organs 7: 378-385, 1961.

75. SHAH-MIRANY, J., NAJAFI, H., SERRY, C., CALLAGHAN, R. and YANG, J.: Pathophysiological alterations in perfused and nonperfused lungs during cardiopulmonary bypass. Ann. Thorac. Surg. 10: 402-408, 1970.

76. SHINOWARA, G.Y., JOHNSTON, D.M., HERRITT, M.J. and LOREY, E.P.: Spectrophotometric studies on blood serum and plasma. Amer. J. Clin. Path. 24: 696-710, 1954.

77. SHORE, P.A., BURKHALTER, A. and COHN, V.H.: A method for the fluorometric assay of histamine in tissues. J. Pharm. Exp. Therap. 127: 182-186, 1959.

78. SWAN, H. and MEAGHER, D.M.: Total body bypass in miniature pigs post perfusion pulmonary hypertension. J. Thorac. Card. Surg. 61: 956-967, 1971.

79. TAKANO, H., TAKAGI, H., TURNER, M.D., HENSON, E.C., CROWELL, J.W. and AKUTSU, T.: Problems in total artificial heart. Trans. Amer. Soc. Artif. Int. Organs 17: 449-455, 1971.

80. THEWS, G.: Physiologie des Sauerstofftransportes und Pathophysiologie des Gewebs hypoxie. Pp 1-10, Bericht Uber das Hanns Bauer-Gedächtnis - Symposion. 1967, in Mainz.

81. VISUDH-AROM, K., MILLER, I.D. and CASTANEDA, A.R.: Total cardio-pulmonary bypass in puppies: Pulmonary studies. Surgery 68: 878-883, 1970.

82. WARNER, W.A., ANTON, A.H., ANDERSEN, T.W., and SWOFFORD, L.J.: Ventricular fibrillation and catecholamine responses during profound hypothermia in dogs. Anesthesiology 33: 43-51, 1970.

83. WHALEN, R.L., MOLOKHIA, F.A., JEFFERY, D.L., HUFFMAN, F.N. and NORMAN, J.C.: Current studies with simulated nuclear-powered left ventricular assist devices. Trans. Amer. Soc. Artif. Int. Organs 18: 146-151, 1972.

84. WILLIAMS, J.C.P., O'DONOVAN, P.B. and WOOD, E.H.: A method for the calculation of areas under indicator-dilution curves. J. Appl. Physiol. 21: 695-699, 1966.

85. WOODWARD, K.E., STRAUB, H., NOSE, Y. and KOLFF, W.J.: An intra-thoracic artificial heart controlled by fluid amplifiers. Trans. Amer. Soc. Artif. Int. Organs 12: 294-300, 1966.

86. WORTHEN, M., ARGANO, B., SIWADLOWSKI, W., BRUCE, D.W., MacCANON, D.M. and LUISADA, A.A.: Epinephrine-induced pulmonary edema in cross-circulated animals. Jap. Heart J. 10: 142-148, 1969.

87. WORTHEN, M., PLACIK, B., ARGANO, B., MacCANON, D.M. and LUISADA, A.A.: On the mechanism of epinephrine-induced pulmonary edema. Jap. Heart J. 10: 133-141, 1969.

APPENDIX

Deep hypothermia and complete circulatory arrest was employed in order to avoid the initial blood trauma and post-perfusion pulmonary syndromes due to cardiopulmonary bypass. Three calves weighing between 70 and 90 kg had an artificial heart replacement using this technique.

1. Method of Deep Hypothermia and Rewarming

The day before an experiment the animal's body hair was clipped. Thirty minutes after premedication with Trifluopromazine 0.3 mg/kg and Atropine 0.015 mg/kg, halothane was used for induction and intubation. Before cooling catheters for arterial and venous pressure monitoring, blood sampling and fluid administration were inserted through the femoral vessels. Electrodes for electrocardiogram and electroencephalogram, thermistor probes for midesophageal and midrectal temperatures were put in place. After the anesthetic level reached the third plane of the third stage of anesthesia (0.8 - 1.5% halothane and spontaneous respiration), the animal was cooled in an ice water tub (Fig. 42).

10% low molecular weight dextran (10 ml/kg) was given intravenously during the cooling period between 35° and 28°C. At 28°C rectal temperature Trifluopromazine (0.3 mg/kg) and Heparin (1 - 1.5 mg/kg) were given intravenously. After the body temperature fell below 28°C the animal was ventilated manually and halothane was decreased to 0.3 to 0.5%. Cooling was terminated at a rectal temperature between 24°C

and 21°C. The animal was hyperventilated to cause as much respiratory alkalosis as possible prior to circulatory arrest. If this is not done ventricular fibrillation is likely to occur around 22°C rectal temperature. After termination of cooling the body temperature usually drifted down 3° to 5°C. Circulatory arrest time was approximately 50 minutes.

Fig. 42 A calf is cooled in an ice water tub. After the body temperature falls below 28°C, the animal is ventilated manually; and hyperventilated to cause as much respiratory alkalosis as possible prior to circulation arrest.

About one minute before commencement of pumping with an artificial heart the animal was mechanically ventilated at a low frequency. After completion of the surgical procedure, the animal was transferred into a 42°C water tub. Hyperventilation was employed during rewarming. Correction of acid-base imbalance was generally unnecessary. Rewarming was terminated at a body temperature between 35° and 37°C (Fig. 43).

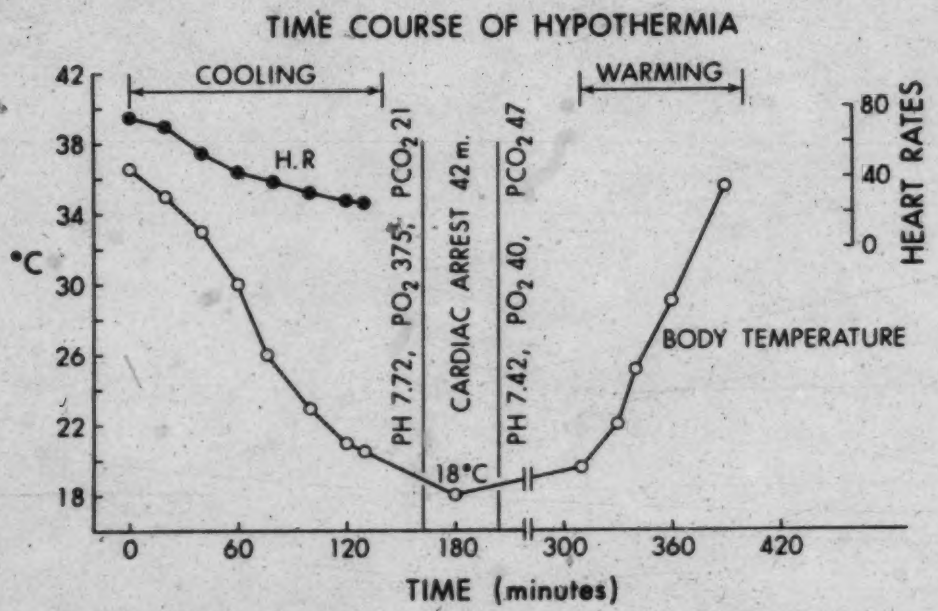

Fig. 43 Body temperature course during heart replacement with deep hypothermia.

2. Surgical Procedure and Pumping

After cooling was terminated the animal was very gently transferred onto the operating table and placed in the supine position. The chest was entered through a midline sternotomy. Umbilical tapes were passed around the superior and inferior vena cava, azygous and hemi-azygous veins, pulmonary artery and the aorta. After blood flow to

and from the heart was interrupted by occluding the vessels with umbilical tapes passed through tygon tourniquets, resection of heart, anastomoses, and priming of the artificial heart with ACD blood were performed in the same manner as was done when using cardiopulmonary bypass. As soon as both ventricles were fully primed, the tourniquets around the vessels were released, and both ventricles were pumped at low pressure and at a low pump rate. During rewarming fluid imbalance was corrected. As body temperature rose, the pump pressure and rate were increased. At approximately 28°C protamine sulphate was given until the whole blood clotting time returned to 10-12 minutes. After the termination of rewarming, the animal was transferred to a specially constructed mobile cage.

3. Results

The natural heart in three calves was replaced with a sac-type artificial heart. During the replacement deep hypothermia was used to arrest circulation. The lowest rectal temperature was between 17.5 and 21°C. The complete circulatory arrest time was between 48 and 52 minutes, during which time the total artificial heart replacement was accomplished. During rewarming these three animals had good reflexes in response to sound and light and breathed spontaneously with a tidal volume of 550 to 700 ml. This was a better result than that obtained using cardiopulmonary bypass.

One of the three animals died of convulsion caused by thromboembolism immediately before termination of rewarming. At postmortem examination both ventricles contained fresh red blood clot which was attached to sac walls in the vicinity of the valves. Various sizes of

thromboemboli were found in the brain, lungs and kindeys. Serious congestion, edema and hemorrhage were seen in the regional infarct of the lungs (Table 13).

Two of the three animals were sacrificed due to severe metabolic acidosis after 9 and 13 hours of pumping respectively (Table 13). During rewarming they developed combined respiratory and metabolic alkalosis and at the termination of rewarming they had respiratory alkalosis with renal compensation. Then metabolic acidosis developed (pH 7.30, pCO_2 28 mm Hg, and base excess -12 milliequivalents per liter) (Fig. 44). The cardiac output was 3 liters per min with 35 ml stroke volume about two hours after termination of rewarming and six hours of pumping. The arterial oxygen saturation was maintained at reasonable levels throughout the experiment and the pulmonary arterial pressure was about 20 mm Hg. However, as metabolic acidosis progressed with an accompanying decrease in the arterial pH, the PAP increased gradually and reached 35 mm Hg during the last three hours of pumping (Fig. 45). At autopsy the lungs were in much better condition than were those from experiments using cardiopulmonary bypass.

Blood evaluation at commencement of pumping showed the level of platelets to be much higher and the level of plasma hemoglobin much lower than postcardiopulmonary bypass levels. However, a fall in platelets and an increase in plasma hemoglobin were seen in proportion to pumping time. After 12 hours of pumping, the level of platelets was almost equal to that of experiments using cardiopulmonary bypass (Fig. 46).

TABLE 13

TOTAL ARTIFICIAL HEART EXPERIMENTS USING DEEP HYPOTHERMIA

Exp. No.	Body Weight (kg)	Time of Circulatory Arrest (min)	Rectal Temp (°C)	Heart Type	Duration of Pumping (hrs. min)	A. Cause of death B. Pulmonary findings at autopsy
10	90	48	18	Sac	13:30	A. Metabolic acidosis B. Atelectasis, slight edema
11	70	51	17.5	Sac	4:10	A. Convulsion B. Moderate edema, congestion, thromboemboli
12	72	52	21	Sac	9:30	A. Metabolic acidosis B. Slight edema, atelectasis, thromboemboli

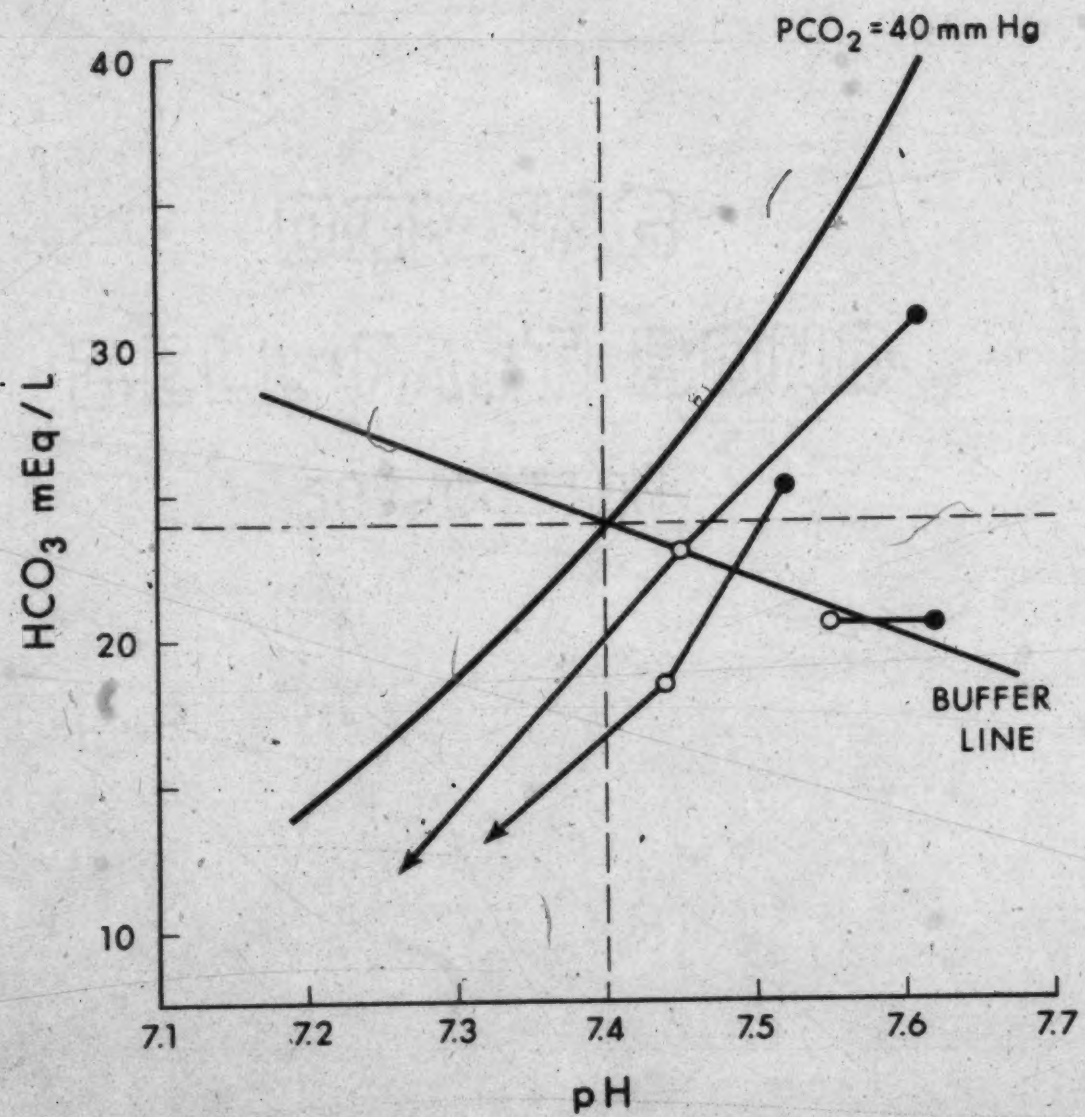

Fig. 44 Postoperative acid-base balance of animals replaced with a sac-type artificial heart using deep hypothermia.

● ; 28-30°C body temperature during rewarming
○ ; after termination of rewarming
← ; about a half hour before termination of experiment

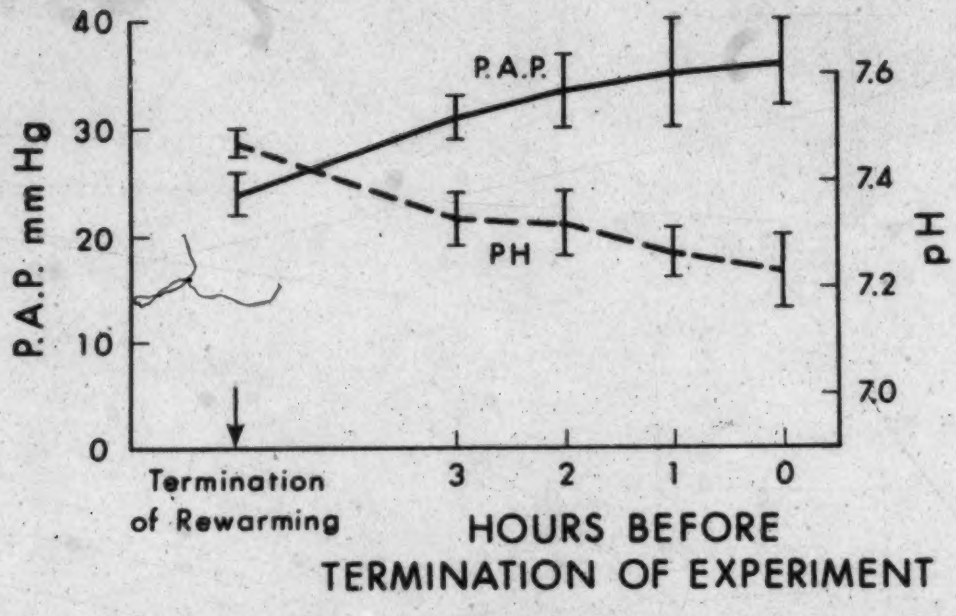

Fig. 45 The change in mean pulmonary arterial pressure and pH at termination of the experiment (using deep hypothermia).

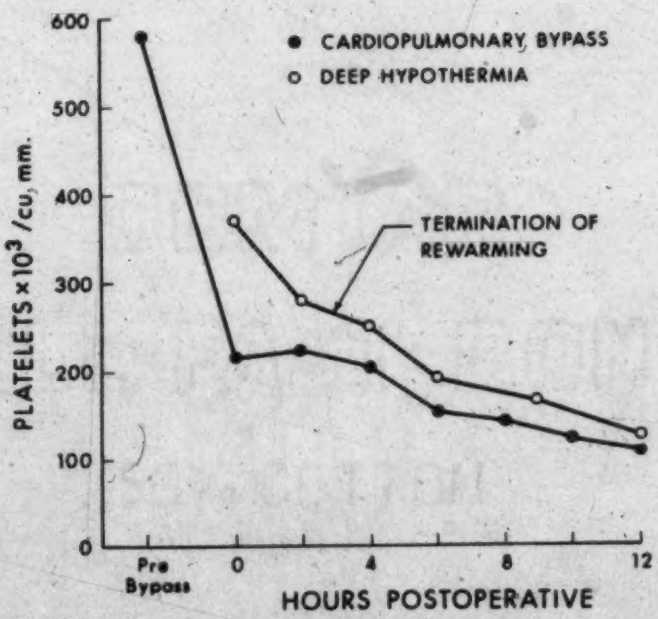

Fig. 46 The change in the postoperative platelets counts from animals using cardiopulmonary bypass and deep hypothermia.

DISCUSSION

Deep hypothermia was not troublesome as a method of support for replacement with a total artificial heart. The body temperature of 20°C or less was safely achieved without side effects, if adequate respiratory alkalosis (pH of 7.6 to 7.8) was maintained during the cooling course[55, 56]; if this is not done various cardiac arrhythmias occur during the cooling process[23]. Auricular fibrillation is one of the most common arrhythmias, but it is not a serious problem. Ventricular fibrillation is the most serious problem[11, 82].

One of the advantages of using hypothermia is the elimination of post-perfusion pulmonary complication. Before the animals developed metabolic acidosis the pulmonary arterial pressure was between 18 and 24 mm Hg and the blood gas examinations showed reasonable levels. However, if the animals suffered from low cardiac output during and after rewarming, they developed metabolic acidosis more rapidly than the animals using cardiopulmonary bypass. At the postmortem examination the morphological changes of the lungs were found to have occurred throughout the whole lungs with a minor degree of severity. On the other hand, in the animals using cardiopulmonary bypass the most serious changes occurred in the lower parts of lower lobes. These findings strongly suggest that the pulmonary deterioration of the animals using cardiopulmonary bypass in the supine position initially develops in the lower parts of the lower lobes[66].

Hypothermia accomplished its purpose of eliminating the initial blood trauma due to cardiopulmonary bypass; however, after 12 hours

of pumping platelets decreased to almost the same level as that of the animals using bypass[44].

5. Summary

Three calves were replaced with a total sac-type, air-driven artificial heart. During the replacement deep hypothermia and complete circulatory arrest was employed. One of three animals died of convulsions caused by thromboembolism. Two animals were sacrificed due to low cardiac output. The lungs from these two animals were in much better condition than lungs from the animals using cardiopulmonary bypass. Initial platelet destruction was not a problem but after pumping with the artificial heart for 12 hours no difference in platelet levels existed between cardiopulmonary bypass and deep hypothermia groups.

VITA

NAME: Tadashi Nishizawa

PLACE OF BIRTH: Tokyo, Japan

YEAR OF BIRTH: 1937

POST-SECONDARY EDUCATION AND DEGREES:

School of Medicine
Chiba University
1956-1962 B. Med.

Postgraduate Course
School of Medicine
Chiba University
1962-1963 M.D.

Postgraduate Course
School of Medicine
Chiba University
1963-1967 Ph.D. (Japan)

Faculty of Medicine,
University of Alberta,
Edmonton, Canada
1971-1973 M.Sc. (Experimental Surgery)

HONOURS AND AWARDS:

The 3rd Shioda-prize
Japanese Medical Association
1970

MAJOR PUBLICATIONS:

(1) Hemodynamic analysis of isopropyl arterenol in cardiac surgery. Surgical Diagnosis and Treatment, 9: 1235, 1967.

(2) Studies on the liver damage in cardiac surgery. Japanese Journal of Thoracic Surgery, 21: 724, 1968.

(3) Compactation of the discoxygenator, requiring no primed blood. Therapy, 23: 441, 1969.

(4) The use of laughing gas or nitrogen for improvement of prolonged extracorporeal circulation. Journal of the Japanese Society for Surgery, 71: 1176, 1970.

(5) Design and performance characteristic of an artificial heart. Japanese Journal of Thoracic Surgery 26: 191, 1973.

(6) Result of total artificial heart implantation in calves. Japanese Journal of Thoracic Surgery, 26: 271, 1973.

(7) Results of total artificial heart replacement: causes of death and histological examination. Iryo (Therapy in Japan), 27: No. 5, 1973.

(8) Surgical technique for total artificial heart replacement in calves. Annals of Thoracic Surgery, in press.